FACULTY OF MEDICINE AND HEALTH SCIENCES

Mind the others:

An electrophysiological investigation of the psychosocial stress response

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I write this acknowledgments section on July 5th, having just returned from a much too rainy vacation. This part of my PhD dissertation is the last one I will write, a thought that results in both happiness that it is the final part but also a great deal of melancholy as it is the *final part*. The undeniable reality that my journey as a PhD student will be over in a few weeks evokes many feelings but most of all it makes me stand still and look back on the last five years.

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SUMMARY

When a possible threat originating from the social environment is detected, a bodily reaction is initiated by the brain. This reaction helps the individual to adapt to the situation or overcome the imposed challenges and is called the psychosocial stress response. When exposed to social threats sporadically, the psychosocial stress response serves an adaptive function but significant harm can be inflicted on the mental and physical health of the individual if stressors are either too severe (traumatic events) or common (chronic stress). Stress has consequently been linked with nine of the ten most common causes of death, and has also been implicated in the development and progression of several psychiatric disorders including post-traumatic stress disorder, anxiety disorder, depression, and schizophrenia.

The brain is the central organ of the stress response as it detects possible psychosocial stressors and coordinates the subsequent bodily adaptations. The brain is thus a major focus of research. Neural activity is mostly investigated with functional magnetic resonance imaging (fMRI). Its usage has resulted in the identification of several key regions in the brain that are implicated in the psychosocial stress response. fMRI, however, measures neural activity indirectly and has a low temporal resolution which hinders further progression into understanding how exactly the brain responds to psychosocial stressors.

Electroencephalography (EEG), another neuroimaging tool that has a lower spatial but much higher temporal resolution than fMRI and measures neural activity directly, is an excellent investigative means to overcome the aforementioned limitations and advance the research field. Of special interest is electrical source imaging (ESI), a technique whereby the activity measured at the scalp is projected back to the neural sources in the brain, as this analysis method allows us to build upon the vast literature of fMRI and expand our knowledge of the psychosocial stress response.

The objectives of this dissertation are twofold. Firstly the EEG-psychosocial stress research field is evaluated. Secondly, EEG and especially ESI are employed to investigate the psychosocial stress response. Firstly, it is investigated whether a psychosocial stressor in isolation is capable of inducing significant changes in several EEG measures. Secondly, the influence of the employed stress induction paradigm on the subsequent neural activity is studied.

In the study presented in **chapter 2**, the EEG-psychosocial stress research field was systematically reviewed, and the consistency of several commonly employed EEG measures was assessed. Results indicated that three EEG measures, frontal alpha and beta power, and frontal alpha asymmetry, are most commonly used. Subsequent meta-analyses of these measures, however, showed that only frontal alpha power consistently decreases due to psychosocial stressors. Beta power tended to increase and frontal alpha asymmetry varied greatly across studies. Additionally, no study had employed ESI, therefore limiting the possible connections between EEG and fMRI results.

In **chapter 3**, a second systematic review is presented. Here results from studies that investigated event-related potential (ERP) during the Cyberball were evaluated. The Cyberball is a paradigm where participants play a ball-tossing game with two confederates, but are excluded after a certain time. It is the most commonly used paradigm for the investigation of social exclusion, also called ostracism. This study attempts to answer a longstanding question in the field: do these ERP results reflect the activity of an ostracism-specific neural alarm system or do they reflect activity from more general neural systems that might also be activated by other characteristics of the paradigm that are unrelated to ostracism? Results showed that for the most commonly investigated ERP component, the P3b, expectancy violations rather than ostracism best explained the identified changes.

In **chapter 4** it was investigated whether a purely psychosocial stressor is capable of inducing significant changes in several EEG measures. In this study, participants were asked to solve a sequence of cognitively challenging tasks. After each exercise, they received neutral feedback in the control condition but received manipulated negative feedback in the stress condition to induce social-evaluative threat, a well-known psychosocial stressor. Results showed that frontal theta, alpha, and beta power measured at frontal electrodes did not change significantly due to psychosocial stressors alone, but that source level-derived alpha power of the left and right precuneus, and right posterior cingulate cortex increased significantly, indicating a temporary decreased cortical activity in these regions during negative social feedback. This decrease might reflect a regulatory and adaptive process where the focus temporarily shifts to the environment to overcome possible external threats.

In **chapter 5**, the influence of stress induction paradigms on the subsequent psychosocial stress response was gauged. Participants were exposed to both the Cyberball and Montreal Imaging Stress Task (MIST, a paradigm where participants need to solve mathematical equations and receive feedback) on separate days. EEG data directly after the control and stress condition was analyzed and compared, thus investigating the recovery phase of the stress response. Results indicated that when data from both paradigms were analyzed together, no similar or dissimilar neural activity could be identified for any brain region. When both paradigms were analyzed separately, however, activity changes in several brain regions were found that were consistent with previous fMRI and EEG literature. The Cyberball resulted in increased activity in the beta band of the left orbitofrontal cortex, left frontal region, and bilateral temporal regions while the MIST resulted in increased alpha activity of the left and right precuneus/PCC complex. These results highlight the highly diverse neural response to specific stress induction paradigms. They also question the assumption that the Cyberball is a stress paradigm, as no physiological nor self-report result indicated that participants experienced this paradigm as stressful.

Taken together, the presented studies in this dissertation highlight the complexities of unraveling the neural psychosocial stress response, the significant influence of how exactly the psychosocial stressors are presented, and the possible misconceptions currently present in the field. Crucially, the scientific work in this dissertation points out the significance of ESI as an analytical approach with the potential to bridge the current gap between the EEG and fMRI research lines. This method is likely to significantly contribute to the collective endeavor of better understanding the psychosocial stress response and its influential role in both mental and physical health.

SAMENVATTING

Wanneer een mogelijke bedreiging uit de sociale omgeving waargenomen wordt, zetten de hersenen een lichamelijke reactie in gang. Ze helpt het individu om zich aan te passen aan de situatie en om de bedreiging aan te pakken en wordt de psychosociale stressrespons genoemd. Bij sporadische blootstelling aan sociale bedreigingen heeft de psychosociale stressrespons een adaptieve functie, maar aanzienlijke schade kan toegebracht worden aan de fysieke en mentale gezondheid van het individu wanneer de stressoren ofwel te ernstig zijn (traumatische gebeurtenissen) of te vaak voorkomen (chronische stress). Stress is bijgevolg in verband gebracht met negen van de tien meest voorkomende doodsoorzaken en is betrokken bij de ontwikkeling en progressie van verschillende psychiatrische stoornissen zoals post-traumatische stressstoornis, angststoornis, majeure depressie en schizofrenie.

De hersenen zijn het centrale orgaan van de stressrespons aangezien ze zowel de mogelijke psychosociale stressoren detecteren alsook de daaropvolgende lichamelijke aanpassingen coördineren. Hierdoor zijn ze een belangrijke bron van onderzoek. Neurale activiteit wordt voornamelijk onderzocht met functionele Magnetische Resonantie Beeldvorming (fMRI). Het gebruik ervan heeft geleid tot de identificatie van verschillende sleutelregio's in de hersenen die een rol spelen in de stressrespons. fMRI meet neurale activiteit echter indirect en heeft een lage temporele resolutie, wat verder inzicht in hoe het brein precies omgaat met psychosociale stress belemmert.

Een andere neurologische beeldvormingstechniek, Elektro-encefalografie (EEG), heeft een lagere spatiale resolutie dan fMRI maar meet neurale activiteit rechtstreeks en heeft een veel hogere temporele resolutie. EEG is daarom de ideale techniek om de hiervoor beschreven beperkingen te overstijgen en verder inzicht te brengen in het onderzoeksveld. Vooral het gebruik van elektrische bronlokalisatie (ESI), een techniek waarbij de op de hoofdhuid gemeten neurale activiteit geprojecteerd wordt naar de breinregio's die ze gegenereerd hebben, is hierbij belangrijk: deze analytische methode maakt het mogelijk om de aanzienlijke fMRI-literatuur te benutten en biedt zo de mogelijkheid om de kennis over de psychosociale stressrespons uit te breiden.

De doelstellingen van dit proefschrift zijn tweeledig. Enerzijds wordt de literatuur omtrent EEG en psychosociale stress geëvalueerd en samengevat. Anderzijds wordt EEG en vooral ESI gebruikt om de psychosociale stressrespons te onderzoeken. Eerst wordt onderzocht of een psychosociale stressor in isolatie erin slaagt om significante veranderingen in EEG-maten te induceren. Hierna wordt de invloed van het benutte stressinductieparadigma op de daaropvolgende neurale activiteit bestudeerd.

In de studie die weergegeven is in **hoofdstuk 2** werd het onderzoeksveld omtrent EEG en psychosociale stress systematisch geanalyseerd en werd de consistentie van verschillende vaak voorkomende EEG-maten beoordeeld. Resultaten van dit onderzoek toonden aan dat drie EEG-maten, energie in de alfa- en betafrequentieband gemeten aan frontale elektrodes en frontale alfa-asymmetrie, het meest gebruikt worden. Meta-analyses van deze maten toonden echter aan dat enkel frontale alfa-energie consistent daalt door psychosociale stressoren. Frontale beta-energie had een neiging om te stijgen en frontale alfa-asymmetrie varieerde sterk tussen de verschillende studies. Daarnaast bleek ook dat geen enkele studie ESI benutte, wat de mogelijke verbanden tussen EEG- en fMRI-resultaten limiteert.

In **hoofdstuk 3** wordt een tweede systematische analyse voorgesteld. Hier werden resultaten van studies die event-gerelateerde potentialen (ERP'en) tijdens de Cyberball onderzochten geëvalueerd. De Cyberball is een paradigma waarbij participanten een balspel spelen met twee medespelers, maar uitgesloten worden na een bepaalde tijd. Het is het meest gebruikte paradigma om sociale uitsluiting, ook ostracisme genoemd, te onderzoeken. Deze studie poogde een antwoord te vinden op een aloude vraag in het onderzoeksveld: reflecteren de ERP-resultaten activiteit van een neuraal alarmsysteem dat specifiek ostracisme-gerelateerde informatie herkent of reflecteren ze activiteit van meer algemene neurale systemen die ook door andere eigenschappen van het paradigma geactiveerd kunnen worden? Resultaten toonden aan dat veranderingen in de meest onderzochte ERP-component, de P3b, beter verklaard kunnen worden door het schenden van verwachtingen dan door ostracisme.

In **hoofdstuk 4** werd onderzocht of een psychosociale stressor in isolatie er in slaagt om significante veranderingen in EEG-maten te induceren. In deze studie werd aan participanten gevraagd om een reeks cognitief uitdagende taken op te lossen. Na elke oefening kregen ze neutrale feedback in de controleconditie, maar werd gemanipuleerde negatieve feedback gegeven in de stressconditie om zodoende sociaal-evaluatieve dreiging, een bekende psychosociale stressor, te induceren. Resultaten toonden aan dat energie in zowel de theta-, alfa-, als betafrequentiebanden bekomen van frontale elektrodes niet significant veranderde door

enkel psychosociale stressoren, maar dat alfa-energie van de linker en rechter precuneus, alsook de rechter posterieure cingulate cortex significant toenam, wat duidt op een tijdelijk verlaagde corticale activiteit van deze breinregio's tijdens negatieve feedback. Deze verminderde corticale activiteit reflecteert mogelijks een regulatief en adaptief proces, waarbij de aandacht tijdelijk verschuift naar de omgeving om mogelijke bedreigingen te overwinnen.

In **hoofdstuk 5** werd de invloed van stressinductieparadigma's op de daaropvolgende psychosociale stressrespons onderzocht. Participanten werden op verschillende dagen blootgesteld aan zowel de Cyberball als de Montreal Imaging Stress Task (MIST, een paradigma waarbij participanten wiskunde oefeningen moeten oplossen en feedback krijgen). EEG-data gecapteerd dadelijk na de controle- en stress-conditie werd geanalyseerd en vergeleken, waarbij de herstelperiode van de stressrespons onderzocht werd. Resultaten toonden aan dat het gezamelijk analyseren van beide paradigma's niet leidde tot duidelijk gelijkmatige of verschillende activiteitsveranderingen in de onderzochte regio's. Wanneer beide paradigma's apart geanalyseerd werden daarentegen, werden activiteitsveranderingen gevonden in verschillende breinregio's die consistent zijn met eerder fMRI- en EEG-onderzoek. De Cyberball resulteerde in verhoogde energie in de beta-frequentieband in de linker orbitofrontale, frontale, en bilaterale temporale regios, terwijl de MIST verhoogde activiteit in de alfa-frequentieband veroorzaakte in het linker en rechter precuneus/PCC-complex. Deze resultaten tonen aan dat de neurale respons op specifieke stressinductieparadigma's uitermate divers is. Ze stellen ook de assumptie dat de Cyberball een stressinductieparadigma is in vraag, aangezien geen fysiologische of zelf-gerapporteerde resultaten erop duiden dat dit paradigma als stressvol ervaren werd door participanten.

Samengevat, de bevindingen van de studies die in dit proefschrift voorgesteld worden tonen de complexiteit aan die komt kijken bij het ontrafelen van de neurale psychosociale stressrespons, de significante invloed van de specifieke manier waarop psychosociale stressoren aangebracht worden in onderzoek en de mogelijke misvattingen die aanwezig zijn in het onderzoeksveld. Cruciaal is dat het wetenschappelijk werk in dit proefschrift aantoont hoe belangrijk ESI is als analytische methode om de huidige kloof tussen de EEG- en fMRI-onderzoekslijnen te overbruggen. Deze methode heeft het potentieel om aanzienlijk bij te dragen aan het collectieve streven naar een beter begrip van de psychosociale stressrespons, alsook van zijn invloedrijke rol in zowel de mentale als de fysieke gezondheid.

LIST OF ABBREVIATIONS AND ACRONYMS

AAC	Alpha Attenuation Coefficient
AAC	Amplitude-Amplitude Correlation
ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotropic Hormone
AI	Artificial Intelligence
AIC	Akaike Information Criterion
ALE	Activation Likelihood Estimation
ANS	Autonomic Nervous System
AP	Action Potential
APA	Activating Positive Affect
ASD	Acute Stress Disorder
ASD	Autism Spectrum Disorder
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
AV	Atrioventricular
AVP	Aversive Viewing Paradigm
BDI-II	Beck Depression Inventory-II
BEM	Boundary Element Method
BF	Bayes Factor
BIC	Bayesian Information Criterion
BOLD	Blood-Oxygen Level Dependent
BPD	Borderline Personality Disorder
CB	Counter Balanced
CCS	Cardiac Conduction System
CI	Confidence Interval
CNS	Central Nervous System
CNV	Contingent Negative Variation
CRH	Corticotropin-Releasing Hormone
CSF	Cerebospinal Fluid
CS	Cover Story

CT	Computed tomography
DL	Deep Learning
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
dPAC	Debiased Phase-Amplitude Coupling
DSM-5	Diagnostic
ECG	Electrocardiography
EDA	Electrodermal Activity
EDF	European Data Format
EEG	Electroencephalography
EMM	Estimated Marginal Means
EOG	Electrooculography
EPSP	Excitatory Postsynaptic Potential
ERP	Event-Related Potential
ERQ	Emotion Regulation Questionnaire
ER-SCR	Event-Related Skin Conductance Response
ESI	Electrical Source Imaging
FAA	Frontal Alpha Asymmetry
FC	Functional Connectivity
FDM	Finite Difference Method
FDR	False Discovery Rate
FEM	Finite Element Method
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
FR	Frequency Range
GA-ERP	Grand-Averaged ERP
GLMM	Generalized Linear Mixed Models
GM	Gray Matter
GSO	Gram-Schmidt Orthogonalization
HC	Healthy Control
HCGSN	Hydrocel Geodesic Sensornet
HPA	Hypothalamus-Pituitary-Adrenal
HRA	Hierarchical Regression Analysis

HRV	Heart Rate Variability
Hz	Hertz
IBI	Inter-Beat Interval
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
IPSP	Inhibitory Postsynaptic Potential
K^+	Pottasium Ion
kΩ	Kilo Ohm
LC	Locus Coeruleus
LMM	Linear Mixed Model
LPA	Left Pre-Auricular
LPP	Late Positive Potential
MAST	Maastricht Acute Stress Test
MDD	Major Depressive Disorder
MEG	Magnetoencephalography
MIST	Montreal Imaging Stress Task
ML	Machine Learning
MNE	Minimum Norm Estimation
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
mV	millivolt
μS	microsSiemens
μV	microvolt
ms	millisecond
NA	Negative Affect
NA	Nucleus Accumbens
Na^+	Sodium Ion
NM	Negative Mood
NTQ	Need-Threat Questionnaire
NTS	Need-Threat Scale
OFC	Orbitofrontal Cortex
OSF	Open Science Framework
PA	Positive Affect

PANAS	Positive And Negative Affect Schedule
PASAT	Paced Auditory Serial Addition Test
PCA	Principal Component Analysis
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PNS	Parasympathetic Nervous System
PNS	Peripheral Nervous System
POI	Perceived Ostracism Intensity
PR	Power Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSD	Power Spectral Density
PSS	Psychosocial Stressor
PTSD	Post-Traumatic Stress Disorder
PVN	Paraventricular Nucleus
qEEG	Quantitative EEG
RF	Radio Frequency
RG	Relative Gamma
RMSSD	Root Mean Square of Successive Differences
ROI	Region Of Interest
RPA	Right Pre-Auricular
RSQ	Rejection Sensitivity Questionnaire
SA	Sinoatrial
SAD	Social Anxiety Disorder
SAM	Self-Assessment Manikin
SAM	Sympathetic-Adreno-Medullar
SCL	Skin Conductance Level
SCR	Skin Conductance Response
SCRR	Skin Conductance Response Rate
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Means

SES	Social-Economic Status
SES	Standardized Effect Sizes
SET	Social-Evaluative Threat
SJP	Social Judgment Paradigm
SMD	Standardized Mean Difference
SNR	Signal-to-noise Ratio
SNS	Sympathetic Nervous System
SPA	Soothing Positive Affect
SPECT	Single Photon Emission Tomography
SPT	Social Performance Paradigm
SQAC	Standard Quality Assessment Criteria
SR	Slowing Ratio
STAI	State-Trait Anxiety Inventory
TMCT	Trier Mental Challenge
TSST	Trier Social Stress Test
VR	Virtual Reality
VTA	Ventral Tegmental Area
VU-AMS	VU- Ambulatory Monitoring System
WEIRD	Western, Educated, Industrialized, Rich, and Democratic
WM	White Matter
wMNE	Weighted Minimum Norm Estimation

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Chapter 1

General Introduction

L'enfer, c'est les autres

Jean-Paul Sartre

Homo sapiens is the dominating animal species on earth. This fact is common knowledge but from a physical perspective, it is rather surprising. Comparing physical characteristics with other animal species, homo sapiens is weaker than its closest biological relatives, yet has obtained the capabilities to eradicate any threat that its stronger cousins, and in extension any other animal, might pose. Its dominating presence is so imposing that many animal species have already been eradicated, often because their mere presence is a nuisance to the everlasting expansion of humanity, rather than the possible existential threat they might pose. The often-presented reason for this power imbalance is another well-known fact: homo sapiens is the most intelligent species. While correct, this intelligence gap seems to decrease evermore as researchers worldwide uncover that once-thought unique mental and cognitive abilities of humans are in fact not so unique after all. Compared to chimpanzees and orangutans, toddlers are not better at a large battery of cognitive tasks (E. Herrmann et al., 2007). Other animals such as certain bird and primate species, are capable of using tools (Emery & Clayton, 2009; van Lawick-Goodall, 1968), and even with their much smaller brains, it has been proposed that corvid birds might be capable of higher intelligence, a trait long thought to be exclusive to humans (Nieder et al., 2020; Stacho et al., 2020).

The ongoing research into intelligence has however highlighted a subsection of intelligence that is pivotal for the evolutionary success of the human species: *social intelligence*. In the aforementioned article by Hermann and colleagues (2007), it was shown that while toddlers perform similarly to chimpanzees and orangutans in cognitive tasks related to the physical domain, toddlers outperform both ape species significantly in cognitive tasks related to social cognition. This, and various other research endeavors, have paved the way to our current understanding of humans as so-called ultra-social animals (Tomasello, 2014). Our collective evolutionary triumph is thus not related to our physical capabilities, but rather to our ability to cooperate with one another and form complex social groups and relationships. This cooperative capability, combined with the fact that humans can learn from one another effectively (i.e., *social learning*), is one of the most important factors for our prevailing success as a species (Apicella & Silk, 2019; Boyd & Richerson, 2009; Hill et al., 2009; Rand & Nowak, 2013).

Given that belonging to a social group is advantageous and even necessary for survival, it is of the utmost importance that the individual remains part of the group (Baumeister & Leary, 1995). Humans are therefore highly capable of interpreting social information in their environment and will adapt their behavior when social cues are detected that indicate a possible

threat to their continued inclusion or social status (Baumeister & Leary, 1995; Williams, 2007). Sometimes, however, social stimuli might demand adaptations from the individual that exceed their direct mitigating capabilities and when such stimuli are encountered, a so-called *stress response* is evoked (Lazarus & Folkman, 1984). A stress response can thus be understood as an adaptive bodily reaction that prepares the individual to overcome the imposed social challenge (called *psychosocial stressor*) as best as possible (McEwen, 2009; McEwen & Gianaros, 2011).

Psychosocial stress and the subsequent stress response has been the subject of much research (Cooper & Dewe, 2008; Fink, 2010; Robinson, 2018). An important reason for this is that stress has a significant impact on both the mental and physical health of individuals (J. T. Cacioppo & Cacioppo, 2014; Epel et al., 2018; Orben et al., 2020; Umberson et al., 2010). Research has shown that stress is linked with nine out of the ten most common causes of death (Kappen et al., 2023), and is furthermore influential in the development and progression of several mental disorders such as depression (Brown et al., 1995; Epel et al., 2018), anxiety disorder (Pêgo et al., 2009; Shin & Liberzon, 2010; Smoller, 2016), and post-traumatic stress disorder (PTSD; Pitman et al., 2012; Sherin & Nemeroff, 2011; Yehuda et al., 2015). Therefore, understanding both how stress affects an individual and how the body responds to stressors is of the utmost importance for understanding and treating a large amount of physical and mental illnesses.

An important aspect of stress research is investigating how the brain responds to stressful stimuli. This focus is logical, given that the brain interprets the sensory stimuli, evaluates their potential threat, and initiates the psychophysiological changes in the body during the subsequent stress response. It can thus be considered the central organ of the stress response (McEwen, 2007, 2009; McEwen & Seeman, 1999). This research is mostly conducted using non-invasive neuroimaging techniques of which *functional magnetic resonance imaging* (fMRI) and *electroencephalography* (EEG) are the two most commonly employed. fMRI is mainly used to address the question of *where* in the brain stressful stimuli are processed and the stress response is controlled, while EEG is more often used to evaluate *when* brain functions are active and how these neural processes change over time.

This dissertation, comprised of six chapters, focuses on the usage of EEG to measure the psychosocial stress response in healthy, adult populations and provides both a critical evaluation of the current state of the EEG-psychosocial stress research field. It also extends the field by assessing the possible added value of *electrical source imaging* (ESI), an EEG imaging method that, contrary to the more commonly applied sensor-level analyses, allows the investigation of individual brain regions. ESI thus has the potential of briding the current gap between fMRI and EEG research by combining the vast fMRI literature with the high temporal resolution inherent of EEG.

In **chapter 1**, the main concepts and employed methods of the dissertation will be outlined. The first section of this chapter is devoted to delineating *psychosocial stress* by firstly providing a formal definition and (for this dissertation) the most important stimuli (i.e., *stressors*) that evoke a psychosocial stress response, as well as the commonly employed paradigms that incorporate these stressors. Additionally, the question *why* psychosocial stress is so important as a research subject is addressed by summarizing its clinical relevance. Next, the neurophysiological pathways through which the stress response is instigated and controlled are described. The second section is devoted to the various ways in which the psychosocial stress response can be measured. This section is divided into two parts: the measurement of how *the body*, and how *the brain* responds to stressful stimuli. Given the large amount of available measurement options, these sections will be limited to the employed methods in the subsequent chapters, but additional methods will be briefly discussed if they are relevant for the interpretation of the subsequent chapters. Regarding the bodily measurement of the psychosocial stress response, the focus will be given to *electrodermal activity* (EDA) and *electrocardiography* (ECG), where the underlying rationale of how psychosocial stress affects these measures will be given, followed by an explanation of how the quantitative measures are obtained and computed. The section outlining how psychosocial stress-related neural activity is measured starts with a summary of fundamental concepts related to the brain and neural communication, followed by a detailed explanation of the underlying principles of the two previously mentioned neuroimaging methods: fMRI and EEG. Considering that EEG is the main neuroimaging modality of interest in this dissertation, this part of chapter 1 is most elaborate. The underlying principles, the preprocessing steps, the ESI computational steps, and the three main EEG analysis methods that are used throughout this dissertation; event-related potential (ERP), EEG spectral power, and functional connectivity (FC) are described in detail.

The final section of the first chapter states the main objectives of the following chapters and the dissertation in general.

In **chapter 2**, a systematic review of the EEG studies that employ spectral analysis to investigate the effects of psychosocial stress is presented, as well as meta-analyses of the three most commonly employed spectral measures: frontal alpha power, frontal beta power, and frontal alpha asymmetry (Vanhollebeke et al., 2022). **Chapter 3** provides the results of a second systematic review. In this review, studies that analyzed ERPs during the Cyberball paradigm, a commonly employed experimental paradigm for the investigation of social exclusion, also called ostracism, are systematically evaluated. The main research question of this study is whether the ERP results are indicative of an ostracism-specific neural alarm system, or if they reflect other neuronal processes that are possibly evoked by characteristics of the paradigm unrelated to ostracism (Vanhollebeke, Aers, et al., 2023). In **Chapter 4**, results from a first experimental study are presented where a within-subjects design was employed to investigate whether a purely psychosocial stressor, without the presence of additional stressors not related to social interactions, is capable of inducing detectable changes in the commonly employed sensor level measures frontal power in the theta, alpha, and beta band. Subsequently, less employed source level power and functional connectivity measures were also investigated to evaluate the added value of ESI (Vanhollebeke, Kappen, et al., 2023). In **chapter 5**, results from a second experimental study are presented where two psychosocial stressor paradigms, the Cyberball (Williams et al., 2000) and Montreal Imaging Stress Task (MIST; Dedovic et al., 2005), were employed in a within-subjects design. The main objective of this study was to investigate with ESI whether different psychosocial stressors evoke similar neural activity changes in brain regions consistently implicated in the psychosocial stress response, or if differential, paradigm-specific neural activity can be identified. Finally, in **chapter 6**, the obtained results from chapter 2 to 5 are discussed within the larger scope of the research into psychosocial stress. Additionally, limitations, possible future directions, and the final conclusions of this dissertation are presented.

1. Psychosocial stress

1.1. Defining psychosocial stress

Almost any person intuitively knows whether situations are "stressful" and when they are stressed, but defining the antecedents and exact processes themselves is surprisingly challenging. This difficulty of defining "stress" is not unique to the general population but is also present within the field of stress research (Epel et al., 2018). A large reason for this difficulty is the ubiquity of stress. Rather than a clear, specific process evoked by clear, specific stimuli, stress encompasses a large amount of processes and can be evoked by a large amount of events. Stress is furthermore influenced by numerous factors including but not limited to gender (J. Wang et al., 2007), age (Kudielka et al., 2004), race (Forrester et al., 2019; Grobman et al., 2018; Spruill, 2010), social-economic status (SES ; Adler & Snibbe, 2003; Turner & Avison, 2003), previous life experience (Compas & Wagner, 2017; U. Rao et al., 2008), and genetic makeup (Ising et al., 2008; Wüst et al., 2004, 2005).

This ubiquity results in the fact that stress can be defined and measured through a variety of ways, and researchers consequently evaluate stress and its effects differently depending on the specific aspect of stress they investigate. A first distinction that can be found throughout literature is that defining and measuring stress is highly dependent on the discipline of the researcher (Epel et al., 2018). Economists will likely investigate variables such as social-economic status or poverty and their relation to psychosocial stress (G. W. Evans & English, 2002; Kuruvilla & Jacob, 2007), while geneticists will be more inclined to evaluate the influence of mutations in the human DNA on the endocrine components secreted during the stress response (Ising et al., 2008; Wüst et al., 2004). Both research disciplines undoubtedly investigate psychosocial stress and provide valuable insights, yet little to no comparison can be made across these studies and often it is not clear what approach and conceptualization of psychosocial stress best explains the devastating effects it has on humans (Epel et al., 2018; Mauss et al., 2005).

Within the field of psychology and psychiatry, the disciplines in which the research discussed in this dissertation should be interpreted, the most commonly employed definition is presented by Lazarus and Folkman in their seminal book *Stress, Appraisal, and Coping* (Lazarus & Folkman, 1984). Building on earlier work of one of the authors (Lazarus, 1966), a first guideline to stress research is given by declaring that *"Stress is not a variable, but a rubric consisting of many variables and processes"*. Stress is subsequently delineated by setting it

apart from other adaptational processes as otherwise *"stress will come to represent anything and everything that is included by the concept of adaptation"* (Lazarus & Folkman, 1984). A formal definition is later given: *"Psychological stress is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding their resources and endangering their well-being"* (Lazarus & Folkman, 1984).

This definition is accompagnied by a model that proposes how stimuli are evaluated and what conditions result in a stress response (see Figure 1). The model starts with the presence of a stimulus, which can be understood as a change in the detectable internal or external environment of the individual (Gibson, 1960). When the stimulus is present, a so-called primary appraisal (i.e., *"the evaluative process that determines why and to what extent a particular transaction or series of transactions between the person an environment is stressful"*; Lazarus & Folkman, 1984) is started where individual percepts and interprets the stimulus. When the stimulus is evaluated as either positive (i.e., only positive consequences to the well-being) or irrelevant (i.e., no positive or negative consequences to the well-being), no stress response is initiated. When the stimulus is deemed demanding or threatening, however, a secondary appraisal is started. During this appraisal the available resources are analyzed to evaluate whether the threat can be managed or not. If sufficient resources are present, a positive stress response is initiated and coping strategies (i.e., *"the process through which the individual manages the demands of the person-environment relationship that are appraised as stressful and the emotions that they generate"*; Lazarus & Folkman, 1984) are deployed that either focus on resolving the threat itself (i.e., *problem-focused* coping) or the regulation of emotions, thereby changing the relation between the individual and and the threat (i.e., *emotion-focused* coping). If no sufficient resources are available, a negative stress response is generated and the individual is not able to adequatly deploy coping strategies.

Several considerations are needed for the interpretation of this model. Firstly, the model as described above is a simplified version of the original, and leaves out several nuances (Carpenter, 2016; Lazarus & Folkman, 1984). First are the three ways in which stimuli are deemed stressful to the individual after the first appraisal, called harm/loss, threat, and challenge. *Harm* or *loss* refers to damage that that has previously occurred in the individual's life, *threat* refers to anticipated harm or loss, while *challenge* refers to threats that can be overcome by the individual and might result in potential personal gains. Second is the presentation of the primary and secondary appraisals as separate concepts. This seperation is only conceptual and does not impose a difference in significance nor a chronological order

between both stages. Third is the representation of the appraisals as static entities that do not posses variability. In reality both appraisals are highly personal and are subject to a large array of personal and environmental factors. Fourth is the presentation of appraisals and coping styles as mutually exclusive results. In reality many stimuli will evoke multiple appraisals and coping strategies simultaneously (Carpenter, 2016).

Of note is that from this model a separation can be inferred between the stimulus and the subsequent reaction of the individual. From now on the stimulus that has the potential to be stressful will be refered to as a *stressor*, while the response from the individual will be called the *stress response*.

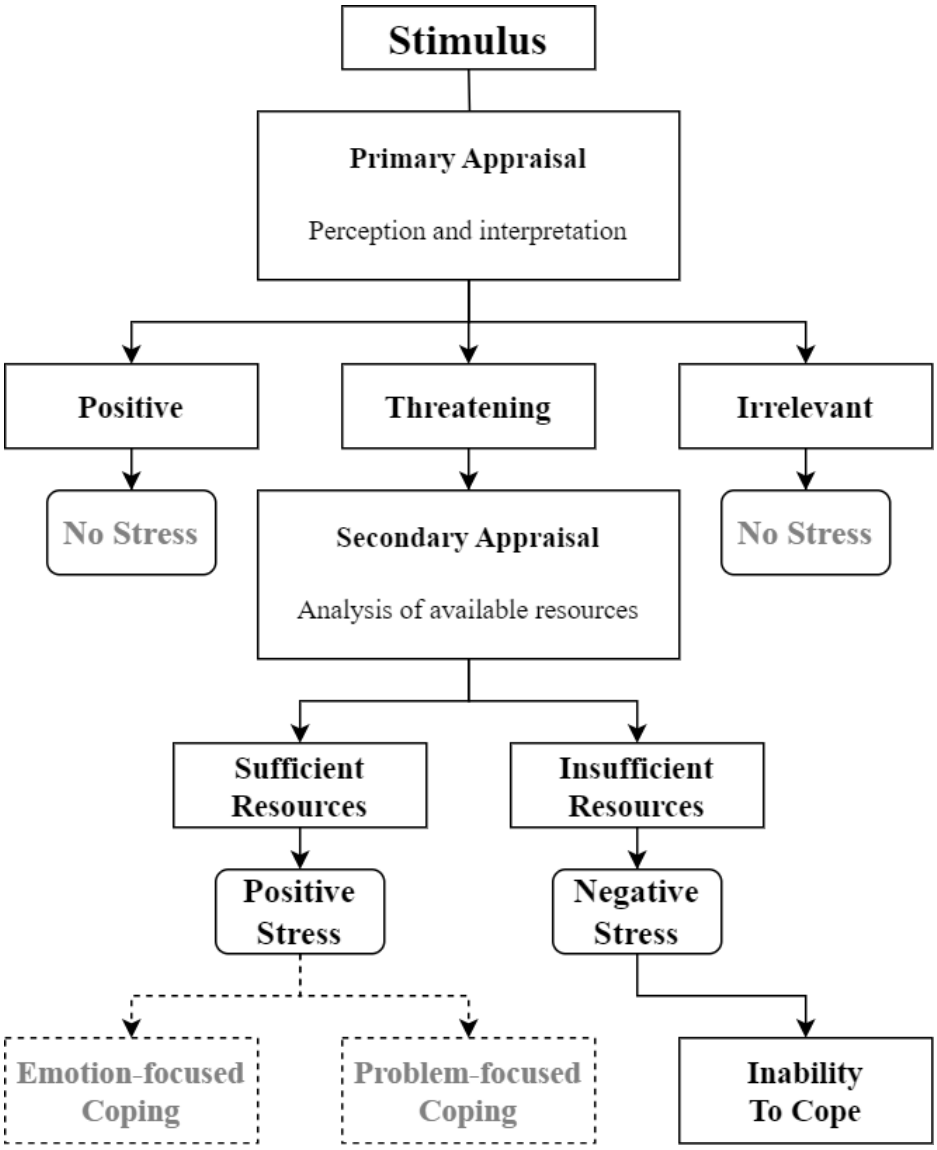

Figure 1: Visualization of the transactional model, adapted from Lazarus and Folkman (1984).

The definition and model of Lazarus and Folkman (1984) provides a solid foundation for defining psychosocial stress and stressors but, for the purpose of this dissertation, lacks specificity. A restriction to the definition and model that can be imposed is the type of stressors that will be considered. Contrary to the description of *psychological stress* by Lazarus and Folkman (1984) which encapsulates a large amount of possible stressors, the studies presented in the current dissertation are related to *psychosocial* stressors. Psychosocial stressors can be seen as a subset of psychological stressors that are limited in origin to those arising from social situations and interactions (Muscatell et al., 2021; Vanhollebeke et al., 2022).

Given the immense complexity of social interactions, researchers have attempted to define more precisely what aspects and stimuli in social interactions might potentially be stressful, and three characteristics have consistently been identified that makes social stimuli potentially stressful: *novelty*, *unpredictability*, and *uncontrollability* (Epel et al., 2018; Koolhaas et al., 2011). Similarly to the appraisals and coping strategies in the model of Lazarus and Folkman (1984), no mutual exclusivity should be assumed regarding these characteristics as many psychosocial stressors exhibit multiple stressful characteristics (Epel et al., 2018).

Taken together, in this dissertation psychosocial stressors are thus defined as *"threatening or stressful stimuli arising from social interactions due to their novel, unpredictable or uncontrollable characteristics"*. A definition of psychosocial stress can further be obtained by slightly adapting the aforementioned definition by Lazarus and Folkman (1984): *"Psychosocial stress is a particular relationship between the person and the social environment that is appraised by the person as taxing or exceeding their resources and endangering their well-being"*.

1.1.1. Phases of the psychosocial stress response

Considering the definition presented above, it should be noted that this conceptualization of psychosocial stress emphasizes the transactional relationship between the individual and their environment. This transactionality allows us to define three phases of a stress response with respect to the actual exposure to a psychosocial stressor: an *anticipatory*, *reactive*, and *recovery* phase. In brief, the anticipatory phase is the time between the occurrence of the stressor itself and the moment the individual becomes aware of the stressor (e.g., lying awake at night because the next day an important presentation needs to be given). The reactive phase is the time that the individual is directly exposed to the psychosocial stressor (e.g., the presentation itself). The recovery phase is the time after direct stressor exposure where the

instigated stress response wanes and the individual returns to their baseline physiological and mental functioning. Of interest here is that the transactional model by Lazarus and Folkman (1984) can be applied to each of these phases, whereby the "Stimulus" in the anticipatory phase is the awareness of an upcoming psychosocial stressor. For a more extensive explanation of the three phases and its relation to EEG, the reader is referred to the introduction of Chapter 2.

1.1.2. Ostracism

One of the most common and well-known psychosocial stressors is *ostracism*. Ostracism lends its name from a democratic process in ancient Greece, showing that it is familiar and even operationalized in social groups (Forsdyke, 2009). The most established researcher regarding ostracism is likely Kipling D. Williams, who defined ostracism as *"ignoring and excluding individuals or groups by individuals or groups"* (Williams, 2007). Williams additionally describes two other psychosocial stressors that are highly similar, yet subtly distinct from ostracism: social exclusion (i.e., *"being excluded, alone, or isolated, sometimes wih explicit declarations of dislike"*; Twenge et al., 2001; Williams, 2007) and social rejection (i.e., *"an explicit declaration that an individual or group is not wanted"*; Leary, 2005; Williams, 2007). The main difference between ostracism and social exclusion/rejection is the explicitness by which the ignoring or excluding is operationalized, although discussion exists as to whether these differences are meaningful from a psychological perspective (Williams, 2007). The main characteristic presented in the previous section that makes ostracism stressful is *uncontrollability*: the individual loses their control over the situation and potentially their place in the social group.

Ostracism threatens four fundamental needs: *belonging*, *self-esteem*, *control*, and *meaningful existence*, and furthermore threatens both the chances of survival and reproduction of the individual (Baumeister & Leary, 1995; Williams, 2009). Given these severe threats, individuals experiencing ostracism consequently adjust their behavior drasticly (Williams & Gerber, 2005; Williams & Zadro, 2001). The immediate reaction to ostracism is emotional: the target feels hurt and might display signs of anger. In the short-term, attempts to restore the threatened needs are made by either strengthening the threatened bonds, taking control of the situation, or maintaining social and cultural buffers (Williams & Zadro, 2001). When ostracism is endured for prolonged period of time, individuals or groups might self-impose the social isolation, engage in learned helplessness or have low self-esteem (Williams & Zadro, 2001). More severe antisocial behaviors have also been linked with ostracism. It has been shown that ostracism has influenced individuals in joining sects or terrorist groups, and has even been

proposed as a potential explanation for mass shootings (Aydin et al., 2010; Ren et al., 2018; Twenge, 2000; Williams, 2007).

As shown in the previous paragraph, the importance of ostracism and its potential devastating effects can hardly be overstated, yet it is commonly employed both by individuals of all ages as well as large social groups (Gruter & Masters, 1986; Williams, 2007). On an individual level, ostracism is best-known as the "silent treatment" and is operationalized by more than two thirds of the population and experienced by more than three quarters (Williams, 2007). Ostracism is further encountered in the workplace (Hitlan et al., 2006; Howard et al., 2020; Williams & Sommer, 1997), school (Williams, 1997; Williams & Zadro, 2001), families (Poulsen & Carmon, 2015; Williams, 2002), and is employed by religious groups and governments (Gruter & Masters, 1986; Williams, 2007). The probability of experiencing ostracism has furthermore been linked with traits such as social status, gender, race, and religious beliefs (Bozin & Yoder, 2008; Howard et al., 2020; Williams, 2007). Considering the evidence, a first conclusion can be formed as to why psychosocial stressors are so important for health and disease: *they are ubiquitous*.

1.1.2.1. The Cyberball

Given the influence of ostracism on health and disease (J. T. Cacioppo et al., 2010), significant efforts have been made to understand its effects on both mental and physical health. This is most commonly investigated with the Cyberball (Williams et al., 2000). The Cyberball is an experimental paradigm whereby participants play a ball-tossing game on a computer with two confederates who are not real but are computer-generated. This makes the amount of inclusion or exclusion predetermined through manipulation of the amount of throws aimed at the participant. The most common employed conditions are an *inclusion* condition wherein the participant receives the ball an equal amount compared to the confederates, and an *exclusion* condition wherein the participant receives the ball rarely or not at all (Williams et al., 2000). For a more extensive description of the Cyberball and the necessary adaptations for conducting EEG research with this paradigm, the reader is reffered to the introduction of Chapter 3, where this paradigm is reviewed with regard to ERP results. This paradigm is additionally employed in the study presented in Chapter 5.

Aside from the Cyberball, ostracism is investigated using a vartiety of paradigms and personality tests, but discussing these in length falls outside of the scope of this dissertation (for an overview, see Williams, 2007).

1.1.3. Social-evaluative threat

Social-evaluative threat (SET) is present when the individual could be judged negatively by others (Dickerson, 2008; Dickerson et al., 2004; Dickerson & Kemeny, 2004). Compared to ostracism, whose main characteristic was uncontrollability, SET is mainly *unpredictable*. Given that no social evaluation can be inferred yet, the individual cannot predict the outcome of the situation. SET is ubiquitous throughout daily life as a myriad of factors related to the self might be judged and, similarly to ostracism SET threatens the fundamental need of the social self (Baumeister & Leary, 1995; Dickerson, 2008). Perhaps the most striking aspect of SET is that it can be perceived by an individual without a preceding environmental stimulus. The individual can experience a stress response before the stressor itself is present as they anticipate the event (i.e., the period in which a person is or could be judged). SET is therefore commonly investigated in all phases of the stress response (see section 1.1.1.) while ostracism is mostly experimentally investigated and analyzed in the reactive and recovery phase. Of note here is that ostracism in real life can also have an anticipatory phase as individuals can anticipate being ostracized due to prior experiences, yet investigating this phase is difficult in laboratory conditions.

Research has shown that a coordinated physiological and psychological response is evoked when individuals are exposed to SET (Dickerson, 2008). Key results from these investigations is that SET exposure results in elevated cortisol (see section 1.2.; Dickerson, 2008; Kirschbaum et al., 1992) and proinflammatory cytokine levels (mediators of the immune system; Coico, 2021), and leads to increased negative affect and self-consious emotions (Gruenewald et al., 2007; Leary, 2007). Differences between individuals regarding how they *perceive* and *respond* to SET have also been identified (Dickerson, 2008; Dickerson & Kemeny, 2004). Several studies have linked personal traits such as self-esteem (B. L. Hughes & Beer, 2013), social anxiety (Ononaiye et al., 2007) or rumination tendency (Vrshek-Schallhorn et al., 2019) to differential reactions to SET. Suspectibility to SET has further been linked with the development of mental disorders such as anxiety disorder (Wong et al., 2020) and depression (Silk et al., 2012).

1.1.3.1. The Trier Social Stress Test

The best-known paradigm for the investigation of SET is the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). In this experimental paradigm participants are told that they need to apply for a fictious job as an applicant and will be interviewed by up to three individuals that are experts in non-verbal communication. Directly afterwards the participant prepares (usually ten minutes; the anticipatory phase) for the upcoming interview but cannot write anything down. Once the preparation time is finished, participants are led to another room where the "interview committee" is seated. The participant is asked to start the interview which will last five minutes (the reactive phase) and during the presentation the committee does not show any signs that might encourage the participant. If the participant stops talking they are reminded that there is more time. If the participants stops a second time the interviewers are silent for 20 seconds and then start asking predetermined questions. When the interview is over the participant is asked to serially subract 13 from 1022 for five minutes (the reactive phase). When the participant responds incorrect, one of the inverviewers comments "Stop, 1022" (Kirschbaum et al., 1993). After the interview the participant is asked to remain seated in another room without the presence of other people (the recovery phase).

This paradigm is considered the "gold standard" of psychosocial stress paradigms for a variety of reasons. Firstly, it results in consistent psychological and physiological changes in almost all participants (Goodman et al., 2017; Kirschbaum et al., 1993; Linares et al., 2020). Secondly, the TSST allows researchers to investigate all three phases of the stress response. Thirdly, the TSST employs a naturalistic environment resulting in a high external validity (i.e., results are valid outside of the context of the study; Bracht & Glass, 1968). While highly valuable for psychosocial stress research the TSST has, for the purpose of this dissertation, one significant downside: it is difficult to conduct within the limitations imposed by neuroimaging methods. Although adaptations have been proposed (e.g., Rosenbaum et al., 2018), this complication is often avoided by exposing participants to the TSST and scanning them either during the preparation period or after the complete procedure but these approaches inherently limit the research options to the anticipatory or recovery phase of the stress response. Therefore novel paradigms inspired by the TSST including but not limited to the Montreal Imaging Stress Task (MIST, see below; Dedovic et al., 2005), the ScanSTRESS paradigm (Henze et al., 2023; Streit et al., 2014), the social-evaluative threat paradigm (Wager et al., 2009), and the aversive video paradigm (Noack et al., 2019) have been developed that can be conducted completely within an MRI scanner or while wearing and EEG cap. These developments allow researchers

to investigate all stress phases, but the proposed paradigms are often less naturalistic than the TSST and could be considered less potent due to the absence of direct human interactions throughout the paradigms (Noack et al., 2019). The TSST paradigm has not been employed in the studies presented in this dissertation but given its influence on the field of psychosocial stress research and the MIST paradigm, the reader should be aware of its existence.

1.1.3.2. The Montreal Imaging Stress Task

The Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) is an adaptation of the Trier Mental Challenge Test (TMCT; Pruessner et al., 1999). Learning from the success of the TSST, the MIST also employs SET but presents it in an indirect manner which makes it possible to conduct the MIST in an MRI scanner and thus investigate the reactive phase of the stress response. The paradigm consists of, depending on the implementation, up to three conditions: *rest*, *control*, and *experimental*. The rest condition is self-explanatory: the participant rests and is not actively engaged in any task. This condition serves two important roles. Firstly, a rest condition makes it possible to measure neural activity at the so-called *baseline* or *resting-state* condition of a participant. This condition provides the researcher with a measure of brain activity that is present when the participants are not engaged in any taks (i.e., resting-state activity). Secondly, it makes it possible for the participant to become acquainted with the experimental environment and thus stops (or lessens) an initial stress response as the situation is novel and therefore unpredictable for the participant.

The control and experimental conditions are highly similar but differ in the absence (control condition) or presence (experimental condition) of SET. In both conditions, participants are asked to solve mathematical equations of varying difficulty with the answer always being a number from 0 to 9, resulting in a single needed keystroke for giving the solution. In the control condition the average time needed to solve equations of a specific difficulty level is obtained and after each equation feedback is given that shows whether the participant answered correctly or incorrectly. The control condition serves two purposes. Firstly, it provides the researchers with the necessary information for a successful stress induction: the average needed time to come to a solution. Secondly, it makes it possible to measure neural activity induced by the task but without the presence of psychosocial stressors. Subsequent analyses can therefore more precisely assign neural activity to psychosocial stress which would not be possible if only the rest condition was present as the experimental condition would differ in both the presence of SET and the cognitive challenge provided by the mental arithmetic task.

The experimental condition contains social-evaluative components as throughout the condition two performance indicators are shown. Firstly, a progress bar is shown that shrinks, indicating the remaining time for each equation. The allowed time for each equation is set to 90% of the average needed time in the control condition and if participants answer three consecutive equations correct/incorrect the allowed time is decreased/increased by 10%. Secondly, the performance of the participant is shown on a performance bar where the "average" performance of the group is also shown. Due to the unfair time limit the participant solves between 20% and 45% equations correctly, while the average performance lies between 80% and 90%. Additionally, the participant is reminded by the experimenters that they need to perform equally well as the average group as otherwise their data cannot be used and that their performance is evaluated by the experimenters in real-time (Dedovic et al., 2005). The MIST is employed in chapter 5, and serves as the basis of the paradigm employed in chapter 4.

1.2. Defining the psychosocial stress response

The previous section outlined the theoretical framework of psychosocial stress(ors). This section will discuss how the stress response is initiated by the brain and through which effector systems it adapts the body to overcome the stressor.

The first step of the stress response is the detection and evaluation of stimuli by the brain. Key brain regions involved are the prefrontal cortex (PFC), amygdala, hippocampus, and additional nuclei such as the nucleus accumbens (NA), paraventricular nucleus of the hypothalamus (PVN), and ventral tegmental area (VTA) (Godoy et al., 2018). Generally it is assumed that the amygdala start the stress response by stimulating the hypothalamus to secrete corticosteroids while the PFC is seen as the controlling region (comprised of many subregions, all conducting specific functions; Dayas et al., 2001) that guides the stress response (Godoy et al., 2018; Ochsner & Gross, 2005; Thayer & Lane, 2000, 2009). Of interest here is that the specific brain circuits that are activated are dependent on the type of stressor whereby physiological and psychosocial stressors result in the activation of different, yet overlapping neuronal networks (Dayas et al., 2001). A complete description of these regions and their interactions is beyond the scope of this dissertation, but the interested reader is reffered to the following articles: Godoy et al., 2018; McEwen, 2007, 2009; McEwen & Gianaros, 2011.

This initial coordinated neural activity started by the amygdala leads to the concurrent activation of two major systems: the *Sympathetic-Adreno-Medullar* (SAM) and *Hypothalamus-Pituitary-Adrenal* (HPA) axis (Godoy et al., 2018; Kudielka & Kirschbaum, 2005; McEwen, 2007; Szabo et al., 2012). The fast acting part of the stress response (i.e., a matter of seconds) is orchestrated by the SAM axis in what is commonly called the "fight-or-flight" response. The activation of the sympathetic nervous system (SNS) results in the secretion of epinephrine and norepinephrine by the adrenal medulla, thus increasing their presence in the blood (De Kloet et al., 2005). These hormones subsequently prepare the body to quickly overcome or adapt to the perceived threat by increasing alertness and arousal, increasing the glucose concentration in the blood, increasing oxygen availability through heightened breathing rate, and increasing the heart rate of the individual (Godoy et al., 2018).

The SNS is one of the two branches of the autonomic nervous system (ANS), which has its origins in the hypothalamus (McCorry, 2007; McEwen, 2000; Shields, 1993; McCorry, 2007; Thayer & Lane, 2000, 2009). The other branch, called the parasympathetic nervous system (PNS), is involved in bodily functions related to homeostasis (i.e., the maintenance of a dynamic

equilibrium of the physiological systems in the body; Cannon, 1929) and recovery of the stress response (McCorry, 2007). Both branches of the ANS are dynamically interacting and counteracting the influence of each other. In stressful moments is the SNS more dominant as energy mobilization and high arousal are necessary for quick adaptation while the PNS attempts to counteract these changes in order to maintain homeostasis of the individual (Jansen et al., 1995). When the stress response wanes as well as in moments of rest the PNS is the dominant system and inhibits the SNS (Jansen et al., 1995). This balance between the SNS and PNS results in a highly adaptive system capable of producing appropriate psychophysiological responses to the changing enviroment in which the individual finds itself (Brook & Julius, 2000). Of special interest for this dissertation is the fact that the dynamic changes between PNS and SNS dominance throughout the stress response can be assessed through several physiological measures of which EDA and ECG are two prominent ones (Giannakakis et al., 2019).

The (relatively) slower part of the stress response is orchestrated by the HPA axis, and acts in the order of minutes. The HPA axis is the main system that connects the central nervous system (CNS) and hormonal system, regulates their interaction, is important in the maintenance of homeostasis, and is a key circuit involved in the stress response (Godoy et al., 2018; McEwen, 2009). Once activated, the hypothalamus secretes corticotropin-releasing hormones (CRH) and vasopressin which stimulate the pituitary gland to secrete adrenocorticotropic hormones (ACTH). ACTH subsequently stimulates the adrenal cortex to produce gluco-corticoids, of which *cortisol* is the best-known and most common in humans (Kudielka & Kirschbaum, 2005; McEwen, 2009; Russell & Lightman, 2019). Cortisol is considered the "end product" of the HPA axis and once it is present in the blood it can reach almost any cell of the body. Simplifying the complex interactions and pathways by which cortisol influences the brain and body, two functionalities can be distinghuised. Firstly, cortisol will supress the secretion of CRH and ATCH by inhibiting the hypothalamus and pituitary gland respectively, therefore creating a negative feedback looped aimed at controlling the HPA axis activity (De Kloet, 2013). Additionally, cortisol regulates the adaptation and recovery of the stress response. Cortisol influences energy metabolism and governs the immune and inflammatory reactions evoked during the stress response to avoid damage due to prolonged and uncontrolled activity of these systems (De Kloet et al., 2005).

Taken together, the psychosocial stress response results in the activation of the SNS and SAM axis who prepare the body for immediate reaction, and the activation of the HPA axis who mainly acts as the controlling system of the longer stress response and its recovery.

1.3. Clinical relevance of psychosocial stress

While the previous sections provided a theoretical overview of the concept of psychosocial stres and the main systems involved in the psychosocial stress response, the most important question regarding psychosocial stress remains unanswered: *why is it so important for the health and disease of an individual?*

The answer to this question lies in both the severity and frequency of psychosocial stressors that the individual encounters throughout life and requires a distinction between *acute* and *chronic* stress.

1.3.1. Acute stress

Acute stress refers to a situation where the individual is exposed to a single stressor. Acute stress was most commonly encountered throughout time (e.g., escaping a predator), so the evolved stress systems are best equiped to deal with this form of stress exposure. Acute stress is consequently often seen as the non-damaging aspect of the stress response regarding health complications, but one specific instance has a significant impact on subsequent health, the stress response to severe stressors: *traumatic events*.

Single-event traumatic events, where natural disasters such as earthquakes or volcanic eruptions are obvious examples, can lead to such severe stress responses that the individual is killed directly by the response itself as it induces strokes or heart attacks (Kario et al., 2003; Trichopoulos et al., 1983). Other traumatic events such as mental, physical, or sexual abuse that might not kill the individual instantaneously (although unpredictable during the traumatic experience itself) nevertheless can lead to significant mental and physical health complications later in life (Garfin et al., 2018; Geoffrion et al., 2022). The best-known clinical complications of traumatic experiences are acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) whereby ASD is diagnosed during the 30 days following the traumatic event and PTSD can only be diagnosed after more than 30 days have passed, indicating that the individual exhibits persistent symptoms due to the traumatic event (APA, 2013). More long-term physical complications have also been reported such as lower self-reported physical health and increased mortality, yet these associations are not consistent across studies and require further

investigation (Garfin et al., 2018). Long-term psychological complications are also reported: increased prevalence of depression, anxiety, global distress and even multiple psychiatric disorders have been associated with experiencing traumatic events, highlighting the devastating consequences associated with traumatic exposure (Garfin et al., 2018).

Traumatic events are sadly not uncommon, and are experienced by up to 70% of the world population throughout life (Benjet et al., 2016). Not all individuals that experience traumatic events, however, develop clinical symptoms afterwards and the rates by which subsequent health complications manifest depends on the type of traumatic event. Traumatic events that do not involve interpersonal assault result in subsequent complications in less than one fifth of the subjected sample while complications due to interpersonal assault are higher with the diagnostic and statistical manual of mental disorders (DSM-5; APA, 2013) reporting rates between 20%-50%, although significant variability exists across studies (Geoffrion et al., 2022). Interpersonal trauma was linked with the highest rate of ASD (36%) when compared to accident-related (15.9%), disaster-related (21.9%), life-threatening illness (20.7%), and war-related trauma (14.1%). These statistics again highlight the importance of psychosocial stressors as precursors and moderators of subsequent health (Geoffrion et al., 2022).

1.3.2. Chronic stress

Chronic stress refers to the prolonged, sometimes even subconsious, experience of stress. Experiencing chronic stress thus results in a consistent increased heightened psycho-physiological state (McEwen & Seeman, 1999). Contrary to the acute stress health complications where the *severity* of the psychosocial stressor mainly dictated the damage to the individual, chronic stress leads to health complications due to the *frequency* of psychosocial stressor presence as it results in gradual wear and tear of the body. This process of "wear and tear" with regard to chronic stress is often described by the terms *allostasis* and *allostatic load* (McEwen & Seeman, 1999). Allostasis refers to the normal adaptive stress response, defined as *"maintaining stability (i.e., homeostasis) through change"* (McEwen & Seeman, 1999; Sterling, 1988). Allostatic load is consequently defined as the damage (i.e., wear and tear) inflicted on the body due to the repeated allostasis (i.e., repeated stress responses; McEwen, 1998; McEwen & Seeman, 1999; McEwen & Stellar, 1993). Allostatic load can be seen as dysfunctions of the stress response whereby the normal adaptive activation and subsequent recovery do not function correctly anymore, which is shown in Figure 2. Figure 2A shows the adaptive response indicated by an initial increase in physiological activity, followed by a recovery period where the physiological activity returns to the baseline levels when the stressor is overcome (i.e.,

allostatis). Four allostatic load types have been defined whereby either allostatis is repeatedly elicited due to the presence an excess of novel stressors (Figure 2B), allostasis is not adaptive anymore when confronted with the same stressor repeatedly (Figure 2C), the recovery period does not return to the baseline levels (Figure 2D), or the initial physiological activity does not reach sufficient levels to adequately respond to the stressor (Figure 2E). It should be noted that allostasis and allostatic load do not describe a single physiological reaction but can be applied to multiple biological systems (McEwen & Seeman, 1999). Additionally, not all subfigures in Figure 2 are strictly related to chronic stress but simply reflect different forms of allostatic load.

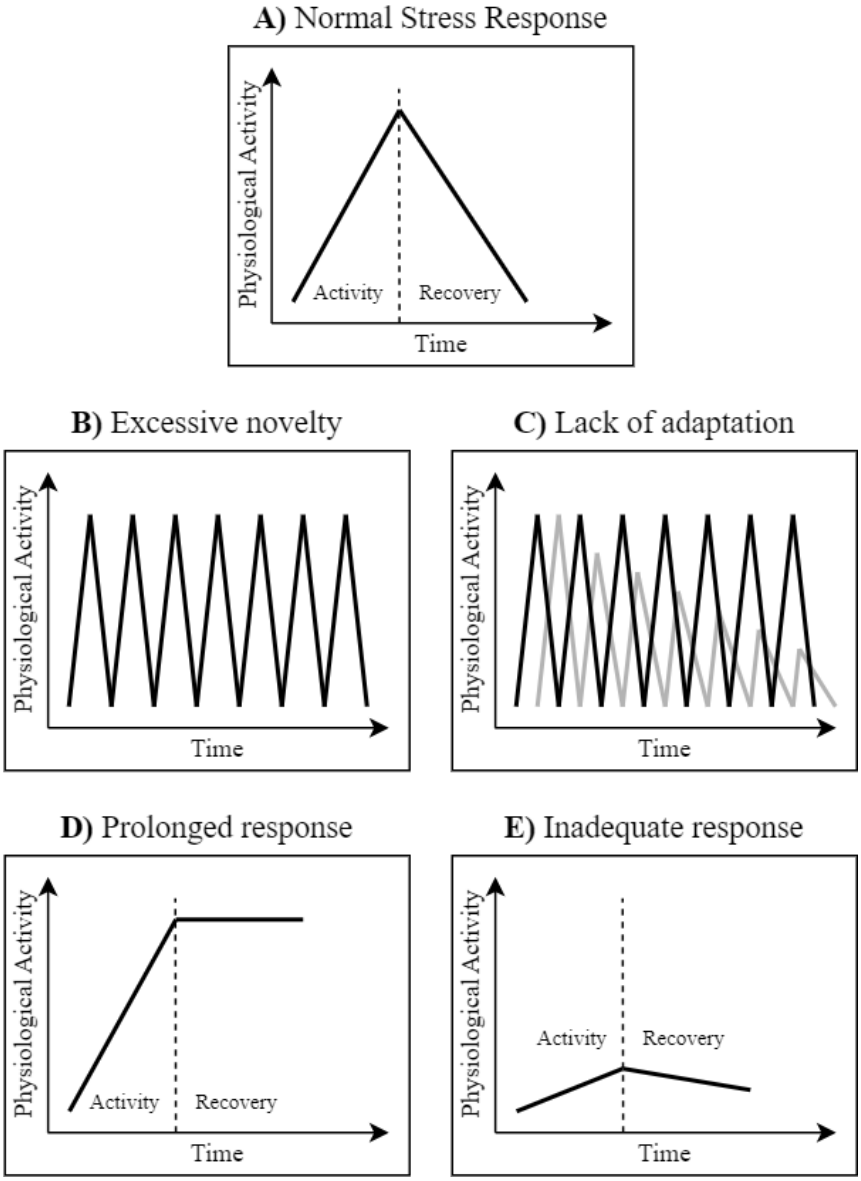

Figure 2: Overview of normal allostatis as a function of physiological activity and the four types of allostatic load. **A)** normal allostatis through time. **B)** repeated allostatis due to excessive novel stressors. **C)** Lack of adaptation given repeated stressor exposure (**Note:** the grey line shows a normal adaptive response). **D)** Prolonged response resulting in an inadequate return to baseline physiological levels. **E)** Inadequate response due to a less than needed increase in physiological activity. **Note:** this figure is adapted from (McEwen & Seeman, 1999).

To understand the pervasiveness of chronic (psychosocial) stress and its influence on mental and physical health, one needs to consider the modern-day challenges the individual faces. Unlike their ancestors, humans in modern times should be less worried about threats from possible predators. Certain aspects from modern life such as the work environment, decreased social connection, economic hardship, increased usage of social media, or existential threats such as the climate crisis, however, play a prominent role in current society while these issues were (partly) absent in earlier times. Allowing a big oversimplification of the underlying complexities, one could propose that modern society "exchanges" direct threats to the life of an individual (although far from absent, see Benjet et al., 2016) for less direct, but more chronic stress exposure.

As stated at the start of this chapter, stress has been shown to play a role in 9 of the 10 most common causes of death (Kappen et al., 2023; Slavich, 2016). Chronic stress has been linked with heart disease (cardiovascular hyperreactivity as a result of HPA-axis and SNS hyperactivity; Bunker et al., 2003), cancer (impaired immune response and chronic inflamation due to consistent HPA activity; Reiche et al., 2004), chronic respiratory diseases (impaired immune system; Hughes et al., 2017), stroke (increased risk of blood cloths, arterial stiffness, and metabolic syndrome; Bhushan et al., 2020), neurodegenerative diseases (accelerated cellular aging; Bhushan et al., 2020), diabetes (increased likelihood of developing metabolic syndrome; Lloyd et al., 2005), kidney disease (due to increased risk of obesity, high blood pressure, and heart disease; Bruce et al., 2015), and suicide (due to increased risk of depression and anxiety, as well as the proposal that suicide results from stressful life events combined with the suspectibility to suicidal behavior; Bhushan et al., 2020; Van Heeringen, 2012). Chronic stress is further implicated in the development and progression of several disorder such as PTSD (as mentioned above), anxiety disorder (Dieleman et al., 2015; Patriquin & Mathew, 2017; Pêgo et al., 2009), and depression, which has the greatest burden of disease across the world (Blackburn-Munro & Blackburn-Munro, 2001; Breslau & Davis, 1986; Briley & Lépine, 2011; Checkley, 1996; Ferrari et al., 2013; Liu et al., 2020; Tafet & Bernardini, 2003).

As shown in the previous paragraph, the importance of chronic stress on the health of the individual cannot be overstated. Two important considerations should be mentioned here. Firstly, while chronic stress has been *implicated* in a multitude of health complications, its causal effects are not yet completely understood, indicating the need for more research. Secondly, the increasing ubiquity of psychosocial stressors in modern life makes it more important than ever as a focus of research.

2. Measuring psychosocial stress

2.1. The bodily psychosocial stress response

The main focus of this dissertation is the neural psychosocial stress response, but in chapter 4 and 5 physiological measures were utilized to evaluate whether the employed paradigms resulted in measurable physiological changes. This section describes the underlying biological principles of these measures, how they are obtained, and addresses how they are affected by the psychosocial stress response. The employed measures are *electrodermal activity* (EDA) and *electrocardiography* (ECG). Additionally, cortisol will be briefly discussed. Although not employed in the work presented in this dissertation, cortisol is seminal in stress research so the reader should be aware of its existence as a measurement tool.

2.1.1. Electrodermal activity

Electrodermal activity (EDA) refers to measurable electrical conductivity changes of the skin (Edelberg, 1972). The skin is a complex organ with many functionalities such as preventing foreign materials from entering the body, thermoregulation and water balance regulation (Montagna, 2012). Considering stress research, the main interest regarding EDA is the fact that sweat glands located on the underside of feet and inside of hands (i.e., plantar and palmar surfaces) are more responsive to psychological than thermal stimuli (J. T. Cacioppo et al., 2007). It is believed that the eccrine glands are most responsible for this given that these are mainly ennervated by the SNS (see section 1.2.; Venables & Christie, 1980). A full description of how EDA changes are generated by the SNS is beyond the scope of this dissertation (the reader is referred to the aforementioned book by Cacioppo and colleague), but briefly stated: psychological stimuli activate the SNS which subsequently stimulates the eccrine sweat glands to release sweat. This increases the amount of sweat near or on the outer surface of the skin, the stratum corneum, resulting in a lower resistivity of the skin that can be measured electrically. Given that EDA is mainly driven by the SNS, it can be seen as a measure of SNS activity.

To measure EDA, two electrodes are placed on or near the hand (in chapter 4 and 5, electrodes were placed on the middle phalanges of the index and middle finger of the left hand). With the knowledge that increased sweat secretion leads to decreased resistance of the skin, applying either a constant voltage or current, one can extract the changing resistance by employing Ohm's law ($R = V.I^{-1}$). EDA is usually expressed as a conductance, which is the

inverse of resistance ($C = R^{-1}$) and has the unit *Siemens*. Normal signal strength is in the range of microSiemens (μS).

An example of an EDA signal is given in Figure 3. As can be seen, EDA data has a low frequency component called the *tonic component* or *skin conductance level* (SCL), which is believed to reflect changes in autonomic arousal (J. T. Cacioppo et al., 2007). Superimposed on the tonic component are several "bumps", called *skin conductance responses* (SCRs). Extracting SCRs can be done by applying a high pass filter, which results in the *phasic component* of the EDA signal. Two forms of SCRs can be defined: *event-related SCRs* (ER-SCRs; SCRs evoked by specific stimuli) and *non-specific SCRs* (NS-SCRs; SCRs occuring without any specific stimulus). EDA data can be analyzed in a variety of ways, and the reader is referred to the aforementioned book by Cacioppo for an overview of analysis options (J. T. Cacioppo et al., 2007). Of interest for this dissertation is the measure *skin conductance response rate* (SCRR), which is employed in chapter 5.

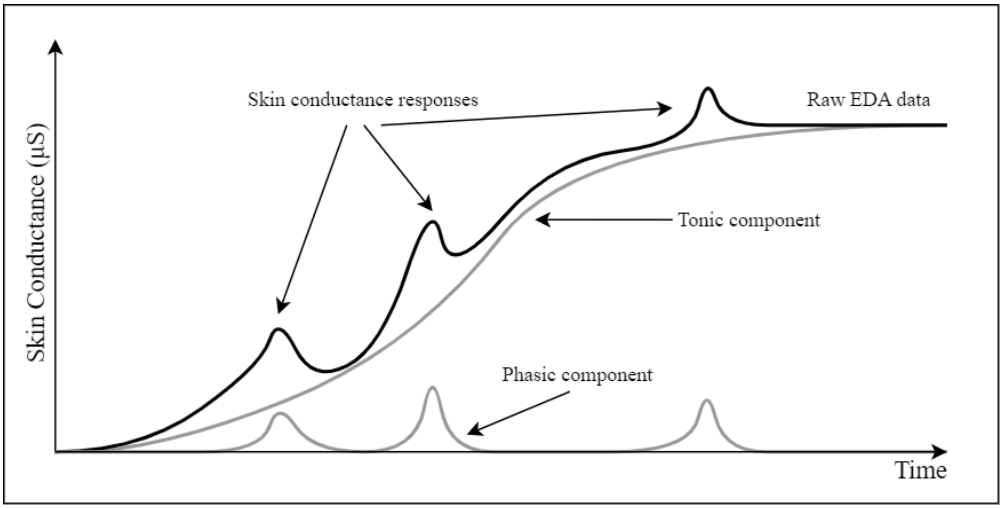

Figure 3: A hypothetical EDA signal. The raw EDA signal is shown in black. The tonic (i.e., low frequency changes through time) and phasic (i.e., the high frequency changes, mostly SCRs) component are shown in gray.

SCRR measures the amount of SCRs in a defined time window and is thus expressed as *number of SCRs/minute*. Although extracted from the phasic component, SCRR is believed to reflect tonic changes in EDA levels and has been linked with the general state of arousal of the individual. Few SCRs/time (i.e., a low SCRR, around 1-3 SCRs/minute) are present during periods of low arousal while higher SCRR (around 20 SCRs/minute) is identified during high arousal (Boucsein, 2012; Braithwaite et al., 2013). Given that psychosocial stress results in higher arousal, it can thus be expected that higher SCRRs will be identified during or after psychosocial stressor exposure (Boucsein, 2012; Braithwaite et al., 2013; Giannakakis et al., 2019).

2.1.2. Electrocardiography

Comprising of four chambers, the left and right atrium, and left and right ventricle, the main function of the heart is ensuring blood circulation, thereby providing nutrients and oxygen to the tissues throughout the body and removing carbon dioxide by pumping blood to the lungs (Guyton, 2006). Blood circulation is conducted by contracting and relaxing the chambers of the heart in a rhythmic manner, and is controlled by the cardiac conduction system (CCS). The CCS starts at the sinoatrial node, located in the myocardium of the right atrium (Downey & Heusch, 2000; Guyton, 2006). The sinoatrial node contains cardiomyocytes, often called *pacemaker cells,* that are capable of spontaneously (i.e., without any external ennervation) depolarizing and generating cardiac action potentials at a rate of approximatly 100 times/second. The sinoatrial node is connected to the atrioventricular node (AV node, called the *secondary pacemaker)* located in the interatrial septum (the tissue seperating the left and right atrium). The AV node is further connected to the *bundle of His* that subsequently diverges into the left and right bundle branches and eventually in the *Purkinje fibers*, which are located in the walls of the ventricles.

Measuring the electrical activity originating to the rhytmic contractions and relaxations of the heart is called *electrocardiography* (ECG). ECG is measured by placing electrodes on the body and measuring potential differences created by the depolarization of the heart muscle cells. Depending on the needed detail of the signal, a variety of electrode positions have been proposed, with the 12 lead placement being commonly employed in clinical care (Houghton, 2019). Less electrodes can also provide adequate, although inferior, ECG signal quality (Fauzani et al., 2013). Figure 4 presents the typical measured potentials of a single heartbeat. The rythmic contractions of the heart start at the SA node, where due to the spontaneous depolarization and subsequent action potentials the atria will depolarize and thus contract, resulting in a small positive deflection in the ECG signal called the P wave. Following the P wave is the QRS complex, which represents the activation of the ventricles. The Q wave reflects the depolarisation of the septum between the left and right ventricle, the R peak reflects the depolarisation of the largest mass of ventricular muscle cells, and the S wave reflects the last phase of ventricular depolarisation (Dupre et al., 2005). Given that the ventricles pump the blood to either the lungs (right ventricle) or to the aorta and subsequently the body (left ventricle) while the atria "only" fill the ventricles, the ventricular contraction is much stronger and thus results in larger deflections in the ECG signal.

Following the QRS complex is the T wave, which represents the repolarization of the ventricles. During rest conditions, this process occurs around 70 times/minute in men and 75 times in women, called the *heart rate*, but significant variability exists between individuals (Guyton, 2006).

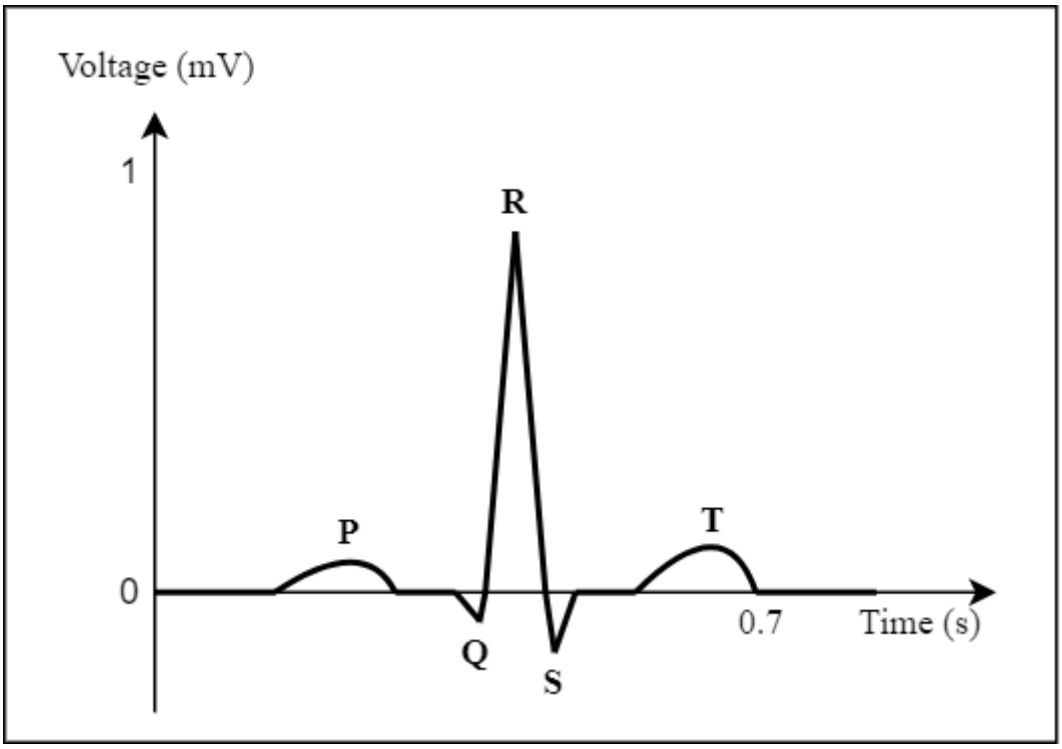

Figure 4: Visualization of a normal ECG waveform. **Note:** the size and timing of each wave is not necessarily representative of a real ECG, as this is only a representation of the different waveforms.

ECG is an invaluable measurement for the diagnosis of a multitude of cardiovascular complications based on the size, timing, and form of each wave as well as the time between the different waveforms (Guyton, 2006). Of interest for stress researchers is the fact that the heart is ennervated by both the sympathetic and parasympathetic branches of the autonomic nervous system (see section 1.2.). This intricate relationship between the SNS and PNS is encapsulated in the *neurovisceral integration* model, proposed by Thayer and Lane (Thayer & Lane, 2000, 2009). Briefly stated, the neurovisceral model describes the pathways through which the brain exerts control on the heart by both the PNS and SNS. The prefrontal cortex, including the orbitofrontal cortex and medial prefrontal cortex, exerts inhibitory control on the amygdala during moments of rest, thus inhibiting the SNS from ennervating and increasing the heart rate. When a stress response is initiated, however, amygdala activity increases (see section 1.2.) while prefrontal activity decreases (Arnsten, 2009). The amygdala now can active the SNS neurons that ennervate the heart and inhibit the PNS neurons. For a full explanation of this model, the reader is referred to the abovementioned articles.

Of interest for stress research is the proposal of one measure, *heart rate variability* (HRV; the variability between the timing of successive heartbeats; Thayer & Lane, 2000, 2009), as a key variable indexing the dynamic relationship between the PNS and SNS because this interplay results in small differences in the timing of successive heartbeats (Thayer et al., 2012; Thayer & Lane, 2000, 2009). High HRV values have been linked with good health and allostasis (Kemp & Quintana, 2013), while low HRV is often found in individuals exhibiting dysfunctions of the ANS or inadequate adaptation to stressors (Kim et al., 2018; Pumprla et al., 2002). Given that HRV reflects the influence of the ANS on the heart, is is commonly used in stress research as *1)* an index of the acute stress response whereby mostly a reduction in HRV is identified during the reactive phase (Castaldo et al., 2015; Rajendra Acharya et al., 2006; Taelman et al., 2009), and *2)* as an evaluation of chronic stress and its influence on several stress-related mental disorders such as major depressive disorder (Carney et al., 2005) and PTSD (Ge et al., 2020), where similarly lower HRV values have been identified in patients suffering from these disorders compared to healthy controls.

HRV can be assessed through a variety of time domain, frequency domain, and non-linear methods (Shaffer & Ginsberg, 2017). For an overview of these measures, the reader is referred to the aforementioned article of Shaffer and Ginsberg (2017), and only the measure employed in chapter 5, the root mean square of successive differences between normal heartbeats (RMSSD), is explained. RMSSD is believed to reflect the vagally mediated changes in HRV, therefore reflecting the influence of the PNS on the heart with low RMSSD values showing PNS withdrawal and high RMSSD values indicating high PNS control (Shaffer et al., 2014). RMSSD computation starts with the extraction of the R-R intervals (i.e., the time between successive R peaks, sometimes called *interbeat intervals* (IBIs), see Figure 5A) from the ECG signal. Next, the successive differences are computed by subtracting RR_{N+1} from RR_N iteratively (see Figure 5B). These differences are subsequently squared and averaged, thus obtaining the average squared value of the differences (unit: ms^2). Finally, the square root is taken, resulting in a final value representing the average difference in R-R intervals (unit: ms). RMSSD is commonly computed from time periods of at least five minutes, but it has been proposed that RMSSD might also provide accurate information on vagal tone for shorter periods of 30 to 60 seconds (Baek et al., 2015; Esco & Flatt, 2014).

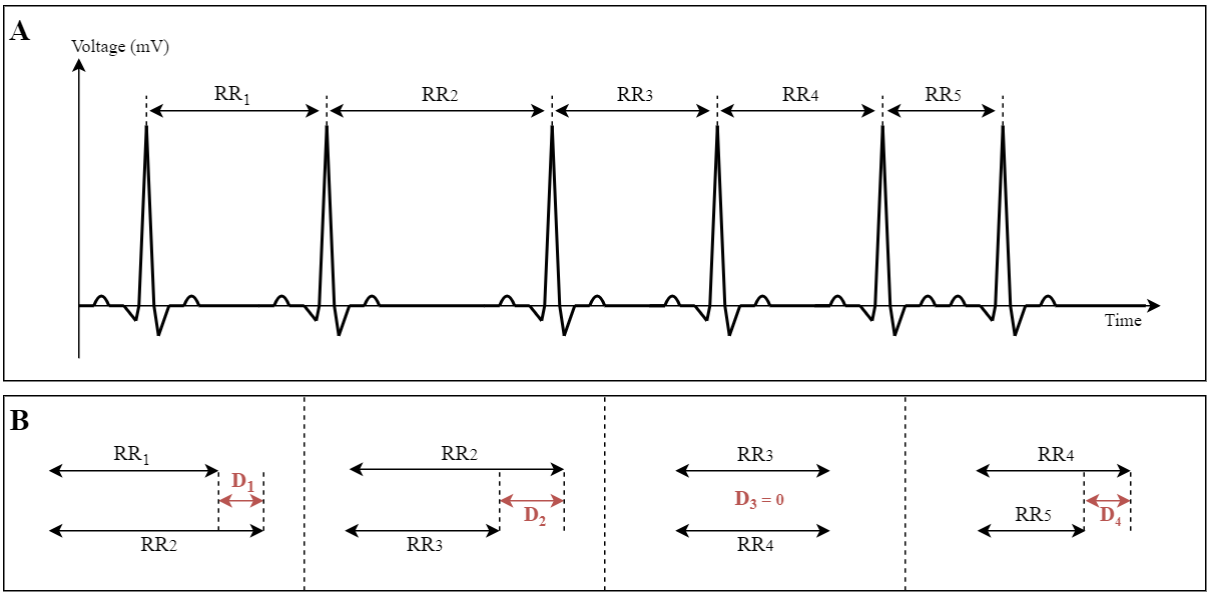

Figure 5: Visualization of the root mean square of successive differences (RMSSD) computation from the ECG signal. **A)** The extraction of the R-R intervals. **B)** The computation of the differences from two successive R-R intervals.

Of note is that RMSSD can assess short-term changes in HRV, but is still limited when assessing direct cardiac responses to stressors. Therefore, some researchers have proposed an adaption of this measure, the *inter-beat interval response* (Gunther Moor et al., 2010; van der Veen et al., 2014). This technique starts similarly as RMSSD, but rather than squaring the differences between R-R intervals, IBI response analysis instead rereferences IBIs to an IBI measured before the presentation of a stimulus (usually the second IBI preceding the stimulus; Gunther Moor et al., 2010; van der Veen et al., 2014). This approach reframes individual IBIs following a stimulus as being either shorter or larger than the reference IBI, and thus reflects either heart rate acceleration or deceleration following the presentation of a stressor (see Figure 6). Considering the neurovisceral model mentioned above, heart rate acceleration reflects increased SNS and decreased PSN activation which occurs when a stress response is initiated (Taelman et al., 2009; Vrijkotte et al., 2000; Ziegler, 2012). Employing this analysis directly after stressor presentation would thus theoretically lead to smaller IBIs, resulting in negative differences compared to the reference IBI (see Figure 6C). Two notes should be made regarding this analysis: it has not been employed as much as other HRV measures so its consistency has not yet been validated thoroughly. Additionally, this analysis results in a measure as a function of IBI number, making comparisons between these results and other measures difficult.

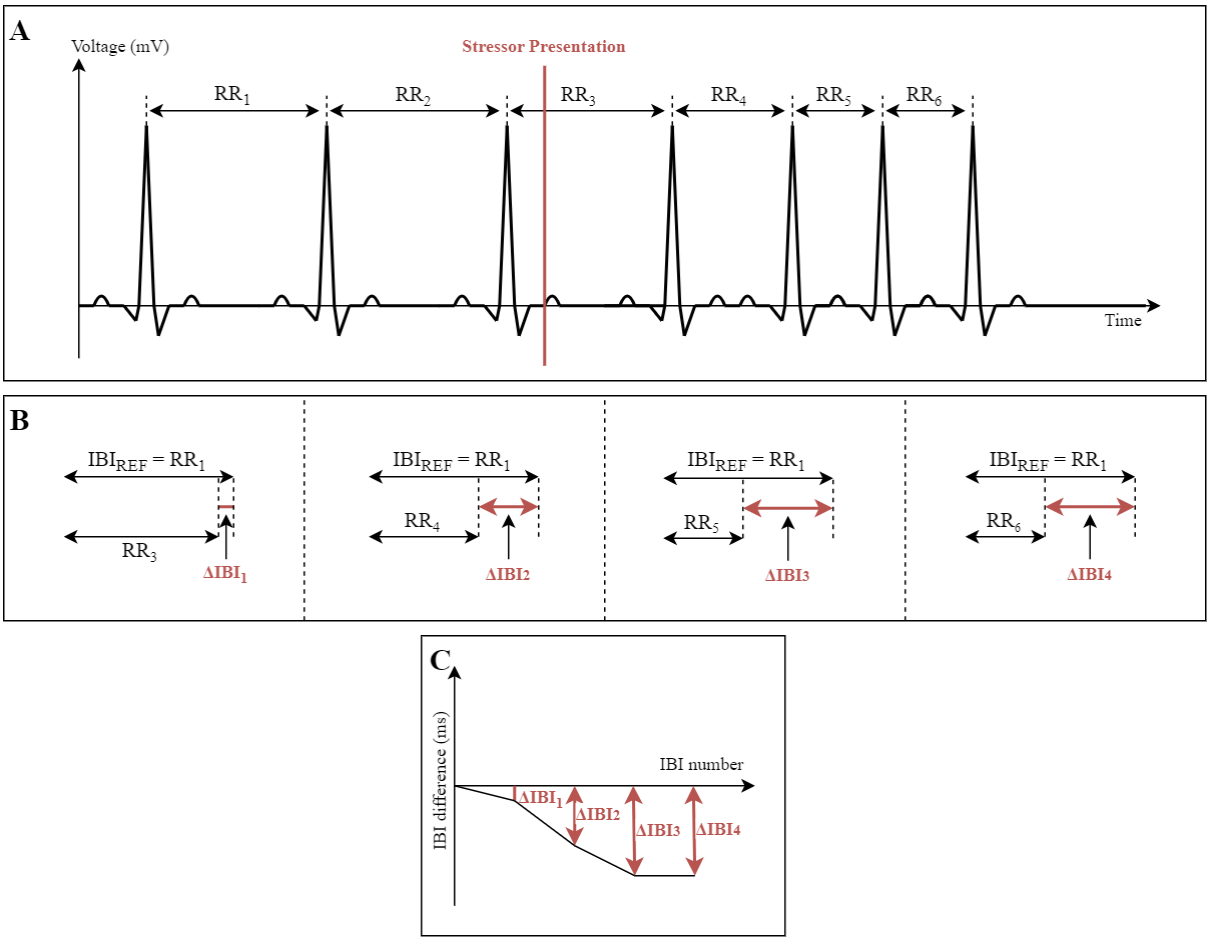

Figure 6: Visualization of the IBI response analysis. **A)** A hypothetical ECG signal where the heart rate accelerates after stressor presentation. **B)** Computation of the IBI differences with regard to a reference IBI (RR_1) resulting in IBI differences (ΔIBI). **C)** Visualization of the different IBI differences as a function of IBI number and IBI difference.

2.1.3. Cortisol

As stated in section 1.2., cortisol is the end product of the HPA axis. Measuring cortisol is therefore a relatively direct gauge of HPA axis activity and is highly valuable in understanding and treating a variety of illnesses such as cardiovascular disease, diabetes, pain syndromes, and psychiatric diseases (Charmandari et al., 2005). Cortisol can be measured from the blood, urine, or hair, but is most commonly assessed through salivary samples in psychosocial stress research given its noninvasivness (Hellhammer et al., 2009). Considering that cortisol is directly related to HPA axis activity, assessing elevated levels of cortisol due to stress paradigms is commonly conducted to evaluate their effectiveness. It is partly because of this that the TSST (see section 1.1.3.1.) is considered the "gold standard" paradigm for the investigation of the psychosocial stress response as elevated cortisol levels are found in almost all participant exposed to the TSST (Goodman et al., 2017; Kudielka et al., 2007; Kudielka & Kirschbaum, 2005). The MIST (section 1.1.3.2.) often shows an significantly elevated cortisol response on group level, but this is sometimes driven by part of the study population (i.e., the "responders"; Dedovic, D'Aguiar, et al., 2009; Dedovic, Duchesne, et al., 2009). The Cyberball (section 1.1.2.1.) is the odd one out, as no consistent elevated cortisol levels are identified during this paradigm (Helpman et al., 2017; Zöller et al., 2010).

Several considerations should be made with regard to cortisol. Firstly, as it is the end product of the slower part of the stress response (i.e., the HPA axis), the elevation of cortisol levels is significantly delayed as it peaks around 30 minutes after stressor exposure (Goodman et al., 2017). Secondly, while cortisol is rightfully one of the best measures of HPA axis activation, it has been shown that salivary samples of cortisol do not necessarily correlate directly with other measures of HPA axis activity such as ACTH (Hellhammer et al., 2009). This lack of consistent associations is also be found when cortisol responses are compared to self-report measures, indicating deviations between the physiological and emotional/ behavioral stress response (Epel et al., 2018). Of note here is that this is not unique to cortisol, and generally physiological and self-report measures correlate poorly (Maus et al., 2005). More importantly, considering the focus of this dissertation, cortisol responses and neural activity are also not necessarily directly linked as the most consistent association between cortisol and neural activity is amygdala activity (not consistently measurable with EEG) while activity in other regions of interest are less clearly correlated (Harrewijn et al., 2020).

2.2. The neural psychosocial stress response

As already numerously stated throughout this chapter, the brain is the central organ of the stress response (McEwen, 2007). Consequently, the brain has been an important part of the research regarding psychosocial stress and is the main organ of interest in this dissertation. The two main techniques employed for this endeavour are *functional magnetic resonance imaging* (fMRI) and *electroencephalography* (EEG). While fMRI is not employed directly in the following chapters of this dissertation, it is the most commonly employed imaging modality in psychologic and psychiatric research (Finn et al., 2023) and studies that employ this technique are heavily relied upon for the selection of brain regions that are investigated in chapter 4 and 5. Therefore the underlying principles and mechanisms of fMRI will also be explained. Before this a summary of brain anatomy, the neuron, and neural communication is provided to better understand the following sections.

2.2.1. Anatomy of the brain

The brain lies within the skull and is connected with the body through the spinal cord. The brain and spinal cord together make up the central nervous system (CNS) while the peripheral nerves are defined as the peripheral nervous system (PNS), to which the ANS belongs. On a macroscopic level, a distinction can be made between gray and white matter. Gray matter is mainly composed of cell bodies and white matter is mostly composed of axons, which connect the different cells (i.e., neurons) both within the brain, connect the brain to the spinal cord, and connect the CNS and PNS. Gray matter is located in different parts of the brain, but most of it is located on the outer surface, which is called the cortex. Gray matter structures located deeper within the brain are also present, but to a lesser extent (although not less important). On a microscopic level, the brain consists of a large number of cells and cell types. Considering fMRI and EEG, neurons are the most important cell type and it is estimated that the brain consists of 86 billion neurons (Von Bartheld et al., 2016). Other cell types in the brain are astrocytes (regulation of the chemical environment), oligodendrocytes (myelin generation for axon insulation), microglia (immune system), and ependymal cells (circulation and production of cerebrospinal fluid). These cells are vital for optimal brain function, and it is estimated that they account for an even greater amount of cells in the brain than neurons, although as of yet no estimate is considered the correct one (Von Bartheld et al., 2016).

2.2.1.1. The neuron

The following section is based on the following works: Cohen, 2014, 2017; Guyton, 2006; van Mierlo, 2013.

The neuron is considered the central cell type of the brain since it is is responsible for transmitting signals and information. Neurons can be divided into three main subparts: the *soma*, the *axon*, and the *dendrites* (for a schematic overview, see Figure 7A). The soma is the cell body where most functionality is located. The soma contains the nucleus wherein the genetic material of the cell is located as well as several organelles necessary for the survival and functioning of the neuron (Guyton, 2006).

The axon is a long projection from the soma (connected at the *axon hillock*) and is the main pathway through which the neuron sends outgoing signals. Although neurons commonly have a single axon, most axons branch out extensively to connect with a multitude of other neurons or target cells. Axon length varies greatly both within the brain as well as in the body, ranging from a few millimeters up to one meter. Given the necessity of fast communication, signals across the axon are transmitted electrically (see below). Therefore, axons are insulated by a phospholipid layer called a *myelin sheeth* (supplied by oligodendrocytes in the CNS and *Schwann cells* in de PNS) which, from an electric perspective, functions as an insulator thus allowing better information transfer. Depending on the length of the axon, multiple myelin sheets are present across its length and the gaps between myelin sheets are called the *nodes of Ranvier*.

The dendrites also extend from the soma but are shorter in length and, contrary to the singular axon, a neuron can have of up to thousands of dendrites. Whereas the main function of the axon was transmitting outgoing signals from the neuron, dendrites transmit incoming signals from other neurons to the soma for further processing. Two neurons connect with each through a synapse, where the *axon terminal* (i.e., the endpoint of an axonal branch) of the presynaptic neuron is located near a dendrite of the postsynaptic neuron. A small gap is present between the axon terminal and dendrite, which is called the *synaptic cleft* (Guyton, 2006).

2.2.1.2. Neural communication

The following section is based on the following works: Cohen, 2014, 2017; Da Silva, 2022; Guyton, 2006; van Mierlo, 2013.

Communication between neurons and between a neuron and target cells is conducted both electronically and chemically. Communication across a single neuron, given the preference of speed, is conducted electronically while communication between neurons is conducted chemically in the synaptic cleft. The preference of chemical communication between neurons is logical as different neurotransmitters (e.g., dopamine, serotonin, gamma-aminobutyric acid) released from the presynaptic axonal terminal result in differential effects on the postsynaptic cell, allowing more diverse and precise forms of communication and reactions (Jabeen & Thirumalai, 2018). Neurotransmitters are essential for correct functioning of the nervous system and dysregulation of these neurotransmitters are heavily implicated in several neuropsychiatric disorders (e.g., serotonin dysfunction in depression; Owens & Nemeroff, 1994), but discussing this form of communication at length falls outside of the scope of this dissertation. For more information regarding neuro-transmitters the interested reader is referred to the following book: Kandel et al., 2000.

Electrical communication in neurons originates from the movement of charged atoms (i.e., ions) and the ions of interest are sodium (Na^+) and potassium (K^+). The cell membrane (i.e., the barrier separating the neuron from its environment) has both Na^+/K^+ pumps and Na^+/K^+ voltage-gated channels, whereby the Na^+ voltage-gated channel opens at -55 mV and closes at +40 mV while the K^+ channels open at +40 mV and close at -80 Mv. At rest (i.e., no signal is transmitted across the neuron) there is a higher concentration of Na^+ ions outside of the cell and a higher concentration of K^+ ions inside the cell due to the Na^+/K^+ pumps. This, combined with the higher permeability to K^+ ions compared to Na^+ ions of the cell membrane, means that the inside of the cell is less positive compared to the outside and results in a so-called *resting potential* of roughly -70 millivolt (mV) (Guyton, 2006).

Electrical communication starts at postsynaptic dendrites. When the presynaptic neuron releases neurotransmitters from the axon terminal they bind to receptors on the dendrite and depending on the type of synapse (*excitatory* or *inhibitory*), the probability of signal transference from the pre- to postsynaptic neuron will either increase or decrease. When excitatory neurotransmitters bind to the receptors, Na^+ channels in the dendrites will open while inhibitory binding results in the opening of K^+ channels. The opening of Na^+ channels (i.e.,

excitation) results in an increased flow of Na^+ ions into the cell resulting in a temporary depolarization of the membrane potential (i.e., the resting potential is less negative) called an *excitatoy postsynaptic potential* (EPSP). When K^+ channels are opened on the other hand, K^+ ions will exit the cell resulting in a hyperpolarization of the cell membrane (i.e., the resting potential becomes more negative), which is called an *inhibitory postsynaptic potential* (IPSP). Of note here is that multiple EPSPs and IPSPs occur simultaneously or in short intervals across the many dendrits of the neuron.

The influx or outflow of Na^+/K^+ ions results, due movement of these ions in the neuron (called *electrotonic conduction*), in changes of the resting potential at the axon hillock. If the amount of EPSPs is larger than the amount of IPSPs, the resting potential at the axon hillock becomes less negative. When the resting potential at the axon hillock reaches -55 mV a sudden, short-lasting hyperpolarization of the cell membrane occurs followed by a repolarization, called an action potential (AP). When an AP is generated, the neuron will "fire", meaning that this AP will propagate across the axon to the axon terminals where they will release neurotransmitters, starting the process over again at the subsequent neurons (for a schematic overview, see Figure 7B). AP generation is a result of the aforementioned Na^+/K^+ voltage-gated channels. Given the decreased resting potential at the axon hillock due to the overabundance of EPSPs, the Na^+ channels located there will open, resulting in a sudden influx of Na^+ ions into the cell which further increases the potential across the membrane. Due to electrotonic conduction, the membrane potential of the axon near the axon hillock will also increase, and the nearby located Na^+ channels will also open. The propagation of the AP can thus be understood as a cascade of rapidly opening Na^+ channels across the axon. The membrane potential will shortly reach +40mV, resulting in a closure of the Na^+ channels and the opening of the nearby K^+ channels. This stops the influx of Na^+ and allows the outflow of K^+, resulting in a quick repolarisation of the rest potential to -80 mV, when the K^+ channels close again. The aforementioned Na^+/K^+ pumps and permeability of the cell membrane will subsequently restore the inital -70 mV resting potential (Guyton, 2006).

AP generation and propagation is energy efficient as the signal is "regenerated" across the axon, but is slower than electrotonic conduction. Therefore neurons with long axons employ both forms of signal transmission. As previously mentioned, long axons are myelinated and across the myelinated parts of the axon, the signal is transferred using electrotonic conduction as the sudden influx of Na^+ ions "pushes" the ions inside the axon further. The signal strength will however decrease as the signal dissapates. Therefore, at the nodes of ranvier AP generation

occurs again thus restoring the signal to its intial amplitude. This combination of AP generation and electrotonic conduction can thus be conceptualized as the AP "jumping" from one node of Ranvier to the next, and is called *saltatory conduction* (Guyton, 2006). This form of signal transfer is both energy efficient and fast, and allows fact reactions to sudden stimuli or stressors.

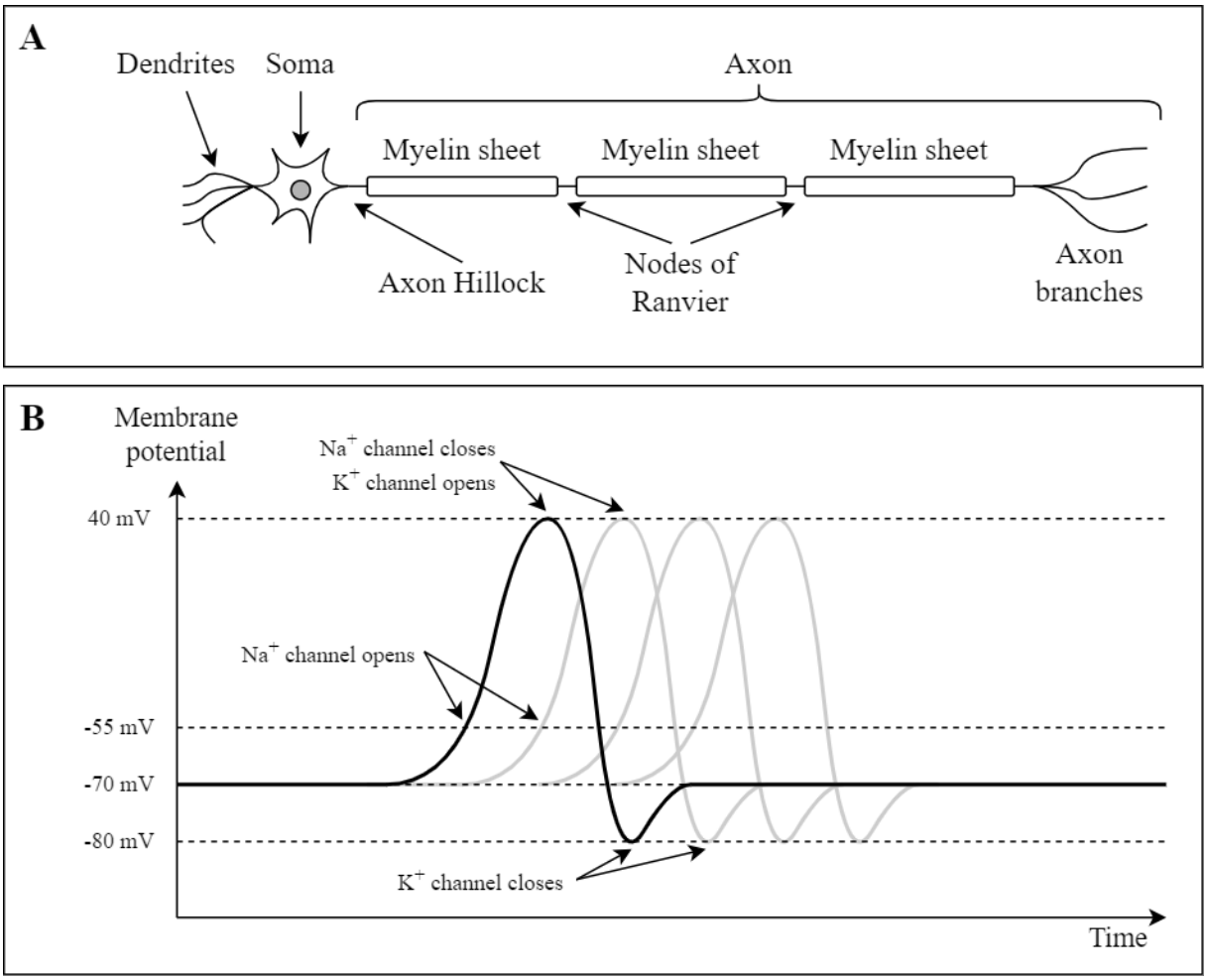

Figure 7: Overview of the neuron and fundamental aspects of neural communication. **A)** Schematic overview of the main parts of a neuron. **B)** Generation of an action potential as a function of membrane potential and time. The gray action potentials represent the generated action potential nearby due to the electrotonic conduction. **Note:** Subsection B was adapted from (van Mierlo, 2013).

2.2.2. Neuroimaging

Neuroimaging refers to a collection of scanning techniques that make it possible obtain "images" of the brain. A first distinction can be drawn between imaging modalities that obtain information about the *structure* (i.e., the composition of cell types, connections between cells, and blood vessels present in the brain as a function of space) and *function* (i.e., the underlying processes such as blood changes, metabolic uptake, and neuronal activity) of the brain. The two main structural neuroimaging techniques are computed tomography (CT) and magnetic resonance imaging (MRI). The best-known functional neuroimaging techniques are positron emission tomography (PET), single photon emission computed tomography (SPECT), near-infrared spectroscopy (NIRS), magnetoencephalo-graphy (MEG), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG).

In brief, CT employs X-rays to obtain brain scans by employing the fact that different tissue types absorb the X-rays differently (i.e. attenuation rates). MRI (explained more in depth below) manipulates hydrogen atoms using strong magnetic fields and radiofrequency waves. PET employs an injected radiotracer (i.e., a molecule of interest labeled with a radionuclide that will emit a positron when decaying) to measure brain function. The best known PET tracer is ^{18}F-FDG (F-fluordeoxyglucose) which shows local uptake of glucose by cells that needs energy (Alauddin, 2012). SPECT works similarly to PET but employs tracers that emit photons, rather than positrons (Khalil et al., 2011). NIRS employs near-infrared light to detect changes in oxygenation levels of blood. MEG measures the magnetic fields at the scalp produced by the electrical currents in the brain (see section 2.1.1.2). fMRI is conducted using an MRI scanner, but measures changes in oxygenation levels of blood. Finally, EEG measures small potential changes on the scalp (or inside the brain when *intracranial* EEG is used) that are produced by neural communication.

The different underlying physical principles and information from various biological processes that can be obtained from these neuroimaging methods has resulted in their widespread adoption in clinical care for the diagnosis of a multitude of illnesses, as well as their well-deserved place as seminal tools in neuroscientific research.

2.2.3. Functional magnetic resonance imaging

2.2.3.1. Physical principles

The subsequent section will give a brief and incomplete overview of the physical principles underlying fMRI, the interested reader is referred to the following book for further information: McRobbie et al., 2017.

Hydrogen atoms account for roughly 62% of all atoms in the human body (Forbes, 2012). The nucleus of a hydrogen atom is a single proton and is thus positively charged, which can be modelled as a small current *I*. According to the circuital law of Ampère, a moving electrical current generates a magnetic dipole field *B* which is defined by its magnetic moment, μ. This magnetic moment can be formulated as the product of the gyromagnetic ratio γ (unit: $Hz.Tesla^{-1}$) and the spin angular moment *S* (i.e., a physical property of subatomic particles defined by the spin quantum number), see formula 1. The gyromagnetic ratio is nucleus specific and has been identified to be 42.57 $MHz.Tesla^{-1}$ for hydrogen.

$$\mu = \gamma . S \quad (1)$$

When hydrogen nuclei are subjected to an external magnetic field, their magnetic moments will try to align with the external magnetic field. This alignment however is not perfect due to the angular momentum, resulting in a precession (i.e., rotation) of the magnetic moment around the external magnetic field. The frequency of this precession is called the larmor frequency, ω_L, which can be obtained by multiplying the magnetic moment of the hydrogen atom and the external magnetic flux density, B_{ext} (unit: Tesla), see formula 2.

$$\omega_L = \gamma . B_{ext} \quad (2)$$

Without an external magnetic field, the net magnetic moment of hydrogen nuclei, M_{hydro} (i.e., the average magnetic field resulting from the summation of the small magnetic moments of individual hydrogen atoms in tissue) is zero as the magnetic moment of individual hydrogen atoms are oriented randomly in the body (see Figure 8A). When hydrogen atoms are subjected to an external, homogeneous magnetic field (B_0) however, M_{hydro} will be different than zero and align with B_0 (see Figure 8B). In this configuration M_{hydro} is static, however, making it impossible to measure.

In order to make M_{hydro} measurable a secondary magnetic field (B_1) oriented perpendicular to B_0 can be introduced that emits radiofrequency (RF) pulses with frequency equal to the larmor frequency. The RF pulses from B_1 change the orientation of M_{hydro} and result in the deviation of M_{hydro} from B_0 and the precession of M_{hydro} at the larmor frequency around B_0. Depending on the strength and duration of B_1, the orientation of M_{hydro} will deviate from its previous alignment with B_0 by a specific angle called the flip angle (θ). The flip angle allows the deconstruction of M_{hydro} into a longitudinal (M_L) and a transverse (M_T) component, whereby M_L is the part of M_{hydro} that aligns with B_0 and is M_T the part of M_{hydro} perpendicular to B_0, see Figure 8C. When B_1 is not applied anymore, M_{hydro} will start to realign with B_0, called relaxation, resulting in an increase of M_L until it equals M_{hydro} (longitudinal relaxation, also called T_1 relaxation) and a decrease of M_T until it is not present anymore (transverse relaxation, also called T_2 relaxation), see Figure 8D. This relaxation will induce currents in nearby electric wires, making it measurable. Longitudinal and transverse relaxation are dependent on different mechanisms that often affect each relaxation type differently, resulting in different relaxation times for each magnetization type respectively. Important for medical imaging is that different tissue types result in different T1 and T2 recovery times, making it possible to distinguish them (Stanisz et al., 2005).

A final issue needs to be considered: all hydrogen atoms in the body will relax following the shutting off of B_1, making it impossible to know from where the measured relaxation is coming from. This can be solved by a third magnetic field, the gradient magnetic field (B_2). The observant reader will have noticed that the larmor frequency (see formula 2) is a function of B_0. When only B_0 is present, all hydrogen atoms will thus precess at the same frequency. When B_0 is modulated by B_2 however, atoms at different locations in the body will precess at slightly different larmor frequencies. As both B_0 and B_2 are externally applied, they can be controlled precisely, making it possible to link specific larmor frequencies to specific spatial coordinates and thus measure the relaxation of specific locations in the body.

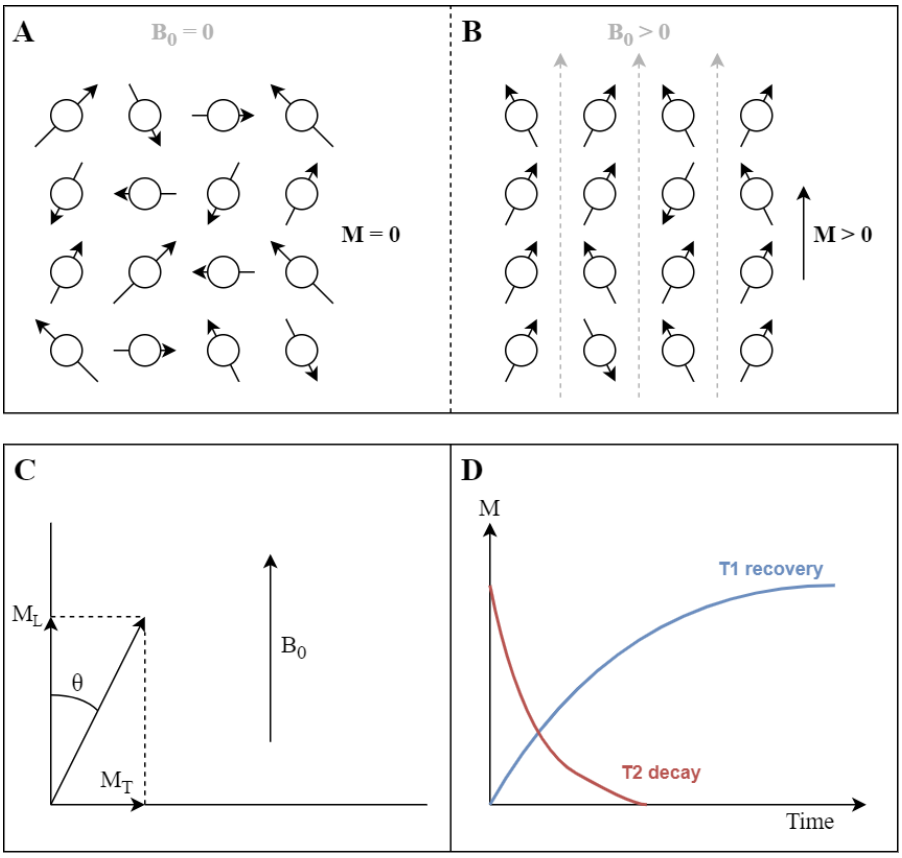

Figure 8: Physical principles of MRI image aqcuisition. **A)** random orientation of magnetic moments of hydrogen atoms, resulting in a net magnetic field of zero. **B)** alginment of magnetic moments of hydrogen atoms due to the presence of an external field, resulting in a nonzero net magnetic field. **C)** Division of M_{hydro} in its longitudinal (M_L) and transverse (M_T) components with respect to the external magnetic field. **D)** Visualization of a T1 recovery and T2 decay with respect to magnetic field strength (M) and time.

It is these techniques that are employed in an MRI scanner. Firstly, a strong homogeneous magnetic field, B_0, is applied which will make the hydrogen atoms in the body align with B_0 and results in the net magnetization, M_{hydro}. Due to the small magnetic forces under consideration, B_0 needs to be very strong to obtain reliable relaxation signals. The high strength of B_0 is the main reason for the high cost of MRI scanners as the magnets need to be cooled using liquid helium and can never be turned off (also explaining the necessary precautions regarding the presence of magnetic objects near the MRI scanner). The gradient magnetic field, B_2, subsequently encodes the spatial location in the MRI scanner by slightly adjusting B_0 so that the evoked larmor frequencies will be a function of their specific location in the MRI scanner. Finally, the RF magnetic field, B_1, will excite the hydrogen atoms, resulting in measurable signals and thus "images". So-called *sequences* whereby the timing, duration and strength of B_1 pulses is varied allows the visualization of various properties of tissue types (Bernstein et al., 2004).

2.2.3.2. Biological principles

The underlying biological principle of fMRI is the idea that active neurons require two components: energy and oxygen (Heeger & Ress, 2002). Neurons do not have much energy stored locally, so this needs to be supplied. The main nutrient for this is glucose which will be transformed into adenosine triphosphate (ATP) through the Kreb cycle by the mitochondria in the active neurons (Finn et al., 2023). Both glucose and oxygen will be delivered through the blood and the increased need of both components results in an increased local blood flow, called the *haemodynamic response* (Heeger & Ress, 2002). Oxygen is transported in the blood by haemoglobin, a protein present in red blood cells. Haemoglobin can exist in to states: oxyhaemoglobin, where an oxygen molecule is bound to haemoglobin; and deoxyhaemoglobin, when no oxygen molecule is bound. Blood flow from arterial vessels will have higher concentrations of oxyhaemoglobin to provide the necessary oxygen to the cells throughout the body, while venous blood will have (relatively) less oxyhaemoglobin as oxygen has been consumed by the cells along the way. Returning to the haemodynamic response, the increased local blood supply is oxygenated blood with a high concentration of oxyhaemoglobin, and actually overdelivers the amount of needed oxygen by the neurons. Taken together, increases in neural activity results in an oversupply of oxygenated blood to the specific region in the brain and thus changes the local oxy- and deoxyhaemoglobin levels temporarily.

Oxy- and deoxyhaemoglobin have different magnetic proporties due the presence or absence of an oxygen molecule, whereby oxyhaemoglobin is diamagnetic and deoxy-haemoglobin is paramagnetic. The relative proportions of oxy-and deoxyhaemoglobin in blood will therefore influence its overal magnetic characteristics, which, considering the previous section, will be measurable by an MRI scanner (Heeger & Ress, 2002; Logothetis, 2008). fMRI thus measures local blood oxygen level changes in the brain, called the *blood-oxygen level dependant* (BOLD) response which is visualized in Figure 9.

The BOLD response follows the haemodynamic response closely, but several considerations are needed. Firstly, BOLD responses to a stimulus are small (relative change of around 2% of blood oxygenation), making it difficult to measure. Secondly, before the peak of the BOLD response an initial dip is detectable, which is believed to reflect the inital increased oxygen consumption of the active neurons (Röther et al., 2002). Thirdly, after the peak of the BOLD response a long undershoot is present before returning to baseline levels. Finally, the peak of the BOLD response is not instantaneous, but is significantly delayed compared to the stimulus presentation.

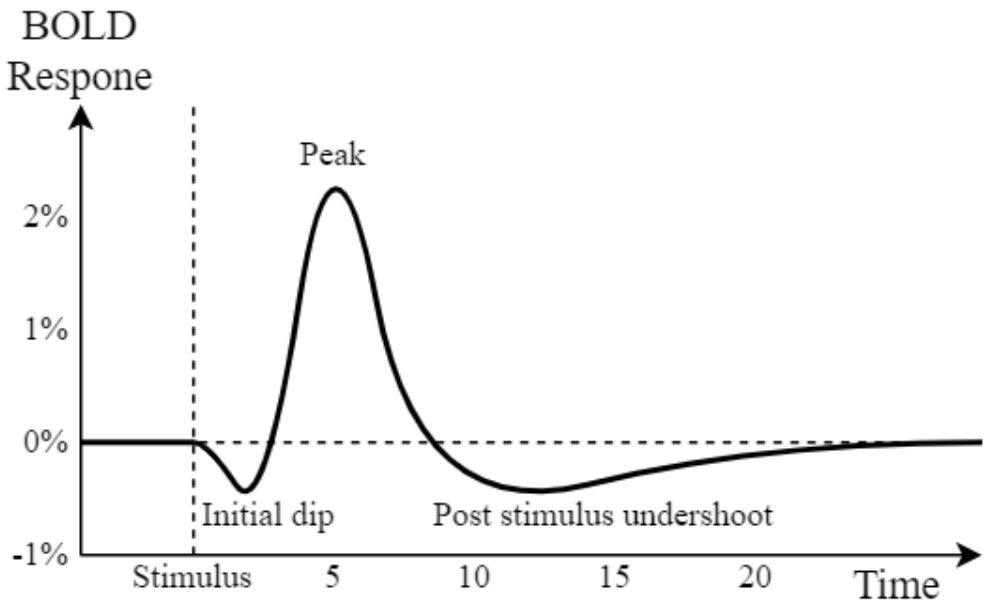

Figure 9: The BOLD response when a stimulus is presented. **Note:** adapted from (Heeger & Ress, 2002).

2.2.3.3. Advantages and disadvantages of fMRI

Since its inception (Ogawa et al., 1990), fMRI has gradually become the main imaging modality in the field of psychology, psychiatry, and neuroscience (Finn et al., 2023). This development has many reasons as fMRI has many advantages compared to other functional imaging modalties. Firstly, fMRI is completely non-invasive and does not rely on radioactive tracers that need to be injected, which is necessary for PET and SPECT imaging. Comparing fMRI to PET and SPECT again shows another advantage of fMRI, it can record brain activity in the order of seconds, making it faster than the aforementioned modalities that record processes on a minute timescale. Secondly, fMRI is capable of measuring whole-brain activity almost instantly, making it possible to evaluate brain activity as a whole throughout time. Finally, and most importantly, fMRI provides high spatial resolution (i.e., the minimum physical distance between objects to measure them independently) where the smallest volumetric unit, a *voxel*, is normally a few cubic millimeters (Finn et al., 2023). Importantly, the spatial resolution is unaffected by the depth of tissue, making it possible to measure activity of brain regions located deep within the brain at the same resolution as more superficial cortical regions.

fMRI has, however, significant disadvantages when compared to other imaging modalities. While its temporal resolution (i.e., the minimum distance in time between events to measure them independently) is higher than PET or SPECT imaging, its is lower than other modalities such as EEG or MEG as the temporal resolution of fMRI is hindered by the delayed

BOLD response. Another disadvantage is the small changes in the BOLD response due to increased neural activity. This makes fMRI a "noisy" technique and thus requires several statistical techniques to correctly identify true BOLD responses from other sources not related to neural activity. These statistical methods have been critisized, for example through the well-known "dead fish" experiment where statistically significant BOLD responses were identified in a dead salmon (Bennett et al., 2009; Lyon, 2017). The final disadvantage is that fMRI measures neural activity *indirectly*, as changes in oxygenation levels of blood, rather than neural activity itself is measured. This indirect measurement has several consequences that are still discussed to this day (Ekstrom, 2010; Heeger & Ress, 2002; Logothetis, 2008; Theriault et al., 2023). Of interest are the assumption that the BOLD response occurs exactly at the place of the active neurons, the limited insights that can be obtained from fMRI as the BOLD response either increases or decreases while the underlying neural processes are more diverse and complex, the fact that the BOLD response amplitude varies across the brain, and the complex relation between brain function and the BOLD response (Finn et al., 2023; Logothetis, 2008).

2.2.3.4. fMRI results regarding the psychosocial stress response

Psychosocial stress researchers have employed fMRI significantly for the identification of the neural signature of the psychosocial stress response. The results can be divided into studies that investigate the *activation* of brain regions, and studies that investigate the *functional connections* between regions. These results will be summarized below with a focus on brain regions that are commonly identified, and are mainly based on the following systematic reviews and meta-analyses (Berretz et al., 2021; S. Cacioppo et al., 2013; Dedovic, D'Aguiar, et al., 2009; Kogler et al., 2015; Mwilambwe-Tshilobo & Spreng, 2021; van Oort et al., 2017; H. Wang et al., 2017). Of note here is that these reviews investigate the psychosocial stress directly, but it should be known that significant research has also been conducted where participants are initially stressed and subsequenly perform tasks. These studies thus investigate the effect of psychosocial stress on specific cognitive or emotional functions (e.g., working memory (Schoofs et al., 2013) but will not be discussed as they fall outside of the scope of this dissertation.

2.2.3.4.1. Activation

Several brain regions have been associated with the psychosocial stress response with varying degrees of consistency. In a recent meta-analysis conducted by Berretz and colleagues (2021), common neural (de)activations due to five different psychosocial stress paradigms: the Cyberball (see section 1. 2.1.1.), ScanStress, MIST (see section 1.1.3.2.), aversive viewing paradigm (AVP ; see section 1.1.3.1.), and social-evaluative threat paradigm (see section 1.1.3.1.) were investigated. Taking all paradigms together, two clusters of increased activation were found: the bilateral anterior insulae with parts of the inferior frontal gyrus (IFG) and claustrum, and one cluster of decreased activation was identified: the right parahyppocampal gyrus and amygdala (Berretz et al., 2021).

Increased activity of the anterior insulae is also found in other reviews. It has been found when the Cyberball paradigm is reviewed in isolation (Berretz et al., 2021; S. Cacioppo et al., 2013; H. Wang et al., 2017), has been shown to be active during the TSST (Dedovic, D'Aguiar, et al., 2009), and even during physiological stress (Kogler et al., 2015). Research has shown that the anterior insula is activated in a wide variety of conditions, ranging from subjective feelings, attention, time perception, visual and auditory perception, visual self-reflection and subjective expectations ((Bud) Craig & D, 2009). This omnipresence of the anterior insulae accross a large variety of tasks makes it difficult to attribute a single function to this region, but many possible roles have been proposed such as the integration of internal emotional states with external sensory stimuli (Menon & Uddin, 2010) or a "gatekeeper" function of executive control (Molnar-Szakacs & Uddin, 2022). Considering psychosocial stress, it has been shown that the anterior insula is connected with the amygdala and hippocampus, indicating a likely role in the regulation and modulation of the HPA axis (Ulrich-Lai & Herman, 2009). Recent work has further delineated distinct subdivisions, each exhibiting specific functionalities (Uddin et al., 2017), making it even more difficult to elucidate the specific role of the anterior insula in psychosocial stress.

The decreased activation of the amygdala and hippocampal is less consistent across studies, a trait that is shared by all involved regions outside the anterior insula. It is identified during the MIST (Berretz et al., 2021; Dedovic, D'Aguiar, et al., 2009) but during the TSST increased, not decreased, activity has been found (Dedovic, D'Aguiar, et al., 2009). Considering section 1.2., the amygdala and hippocampus have a vital role in the instigation of the stress response, making it surprising that these regions show divergent activity patterns across stress paradigms. Several explanations are possible for this: it might be possible that different

psychosocial stressor paradigms result in differential neural responses as they employ different psychosocial stressors. It is also possible that additional aspects of the paradigms not related to psychosocial stress, such as the presence of time pressure or cognitive demanding tasks (e.g., in the MIST), might influence the corresponding neural activation patterns. Finally, it is possible that the limitations of fMRI are partly responsible for inconsistencies across paradigms (see section 2.2.3.3.), showing the importance of additional neuroimaging techniques for further investigation and highlighting the main focus of this dissertation.

Further evidence for divergent neural patterns due to different paradigms is found in the aforementioned meta-analysis by Berretz and colleagues (2021). If the Cyberball is exlcuded from the meta-analysis, more brain regions are consistently (de)activated. Additional regions exhibiting increased activity are the right lentiform nucleus and thalamus, believed to play an important role in the HPA axis (Godoy et al., 2018), the precentral gyrus and posterior insula, again showing the presence of subdivisions in the insular cortex (Uddin et al., 2017), and the inferior/middle temporal gyrus, believed to play a role in emotional cognition and reappraisal (Blair et al., 2007; Ochsner & Gross, 2005). Two additional clusters show decreased activity: the bilateral precuneus and posterior cingulate cortex (PCC), believed to reflect internal focus as a core region of the default mode network (DMN; Cavanna & Trimble, 2006; Johnson et al., 2002; Lou et al., 2004), and the left superior temporal gyrus and parts of the precentral gyrus, which have been linked with emotion regulation (Ochsner & Gross, 2005; Torre & Lieberman, 2018). Similarly to the amygdala and hippocampal gyrus, their consistent (de)activation varies across articles and paradigms (Berretz et al., 2021; Dedovic, D'Aguiar, et al., 2009; Kogler et al., 2015; van Oort et al., 2017; H. Wang et al., 2017).

Two additional brain regions should be mentioned that have not been identified in the meta-analyses described above: the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC). The ACC, and mostly its dorsal subsection, is most commonly associated with the Cyberball and is believed to reflect conflict monitoring and error processing (Bush et al., 2000; Kawamoto et al., 2012; Somerville et al., 2006), although the precise location of activity has been questioned by a recent meta-analysis of Cyberball studies that instead hints at consistent involvement of the DMN during the Cyberball (Mwilambwe-Tshilobo & Spreng, 2021). ACC activity has also been linked with the MIST, although depending on the specific article, either increased or decreased activity has been reported (van Oort et al., 2017). The orbitofrontal cortex has been identified across several paradigms, and is believed to reflect social-cognitive processes (Burnett et al., 2011; Pfeifer et al., 2011, 2013). Interestingly, the orbitofrontal cortex

is found to be increasingly active during the Cyberball (S. Cacioppo et al., 2013; Mwilambwe-Tshilobo & Spreng, 2021; Vijayakumar et al., 2017), while decreased activity is identified during the TSST (Dedovic, D'Aguiar, et al., 2009), and both increased and decreased activity is found during the MIST (Dedovic, D'Aguiar, et al., 2009; van Oort et al., 2017).

Taken together, activation studies regarding the psychosocial stress response identify several involved brain regions including but not limited to the anterior insula, inferior frontal gyrus, amygdala, hippocampus, hypothalamus, parts of the temporal lobe, the precuneus and PCC, the ACC and the prefrontal cortex, most notably the OFC. Aside from the anterior insulae, activity changes are variable across paradigms showing the complexity of the neural psychosocial stress response. Additionally, the co-occurrence of non-psychosocial stressors such as time limits or cognitive tasks seem to further influence the results.

2.2.3.4.2. Functional connectivity

Aside from activation of brain regions, studies have also investigated functional connectivity (FC, the investigation of temporal dependencies between spatially distinct neurophysiological events; Friston, 1994) between commonly implicated brain regions.

One prominent research line is the investigation of functional connections between the amygdala and other regions such as the ACC, PFC, OFC, and mPFC. Keeping section 1.2. in mind, this focus is logical as it is believed that the amygdala initiate the stress response (Godoy et al., 2018; Thayer & Lane, 2000, 2009). Several studies have indeed found alterations in FC between the amygdala and other regions that vary across the phases of the stress response. During acute psychosocial stress, increased FC between the amygdala, ACC and and anterior insula has been found, and is believed to reflect a network that continuously monitors and processes the saliency of incoming stimuli (Seeley et al., 2007). Additionally, increased functional connectivity between the amygdala and the locus coeruleus (LC) has been found, likely indicating the increased vigilance and arousal during stress given that the LC is the main production center of noradrenaline in the brain (de Kloet et al., 2005). Contrary to increased FC between the amygdala and the aforementioned brain regions, inverse FC has been identified between the amygdala and the PFC, most notably the medial PFC (mPFC). This inverse FC likely indicates the temporary decreased control of the PFC during the initial steps of the stress response (Urry et al., 2006).

During the recovery phase of the stress response mPFC-amygdala FC is mostly increased, possible reflecting the heightened control of the PFC on the amygdala following the stress experience (Banks et al., 2007). Increased functional connectivity between the amygdala and hippocampus has also been identified (Buchanan et al., 2001; McEwen et al., 2016; Roozendaal et al., 2009) and this increased FC has further been correlated with cortisol increases (Buchanan et al., 2001). Considering the important role that the hippocampus has in memory formation, it has been proposed that this increased FC reflects the memory consolidation of emotionally salient events after stress exposure. Building on the idea of memory consolidation, increased amygdala-precuneus/PCC FC has also been identified. Considering that the PCC/precuneus has been implicated in autobiographical memory processing (Cavanna et al., 2006; Vann et al., 2009), this results similarly provides evidence for memory consolidation of salient stimuli following stress exposure (Veer et al., 2011).

Amygdala FC with other regions has also been a significant focus in stress-related mental disorders, and several FC alterations have been identified. Decreased amygdala-mPFC FC has been found in individuals with schizophrenia and PTSD compared to healthy controls (Mukherjee et al., 2016; Gilboa et al., 2004). FC changes between amygdala and a variety of prefrontal regions, such as the ventral PFC (Tang et al., 2013; Connoly et al., 2017) and dorsolateral PFC (DLPFC; Lu et al., 2012) has also been found in patients with major depressive disorder (MDD). Patients with anxiety disorder similarly show disruptions in amygdala connection with the PFC, insula, and superior temporal gyrus (Roy et al., 2013). Taken together, the central role of the amygdala and other regions implicated in the stress response and their dysfunctional connectivity is clearly present across several stress-related mental disorders.

Aside from functional connections between regions, fMRI studies have also investigated how brain networks are implicated in the psychosocial stress response. Of special interest is the systematic review of van Oort and colleagues (2017), where the acute stress response is investigated through the lens of three major neural networks: the *salience*, *central executive*, and *default mode* network, that together have been proposed as the *triple network model* where dysfunction in one or more networks results in a wide variety of psychopathologies (Menon, 2011). The salience network is activated if salient stimuli are present or if emotional processing is needed (Hermans et al., 2014; Seeley et al., 2007), and is mainly comprised of the anterior insula, (dorsal) ACC, amygdala, and temporal poles (Goulden et al., 2014; Seeley et al., 2007). The DMN includes an anterior network centered around the medial prefrontal cortex (mPFC),

mostly linked with self-referential processing and emotion regulation and a posterior network comprised of the precuneus/PCC and the parietal lobule, often linked with consiousness and memory processing (Andrews-Hanna et al., 2010; Buckner et al., 2008; van Oort et al., 2017). The DMN is the main network active during the so-called "resting-state", when no task or external stimulus is presented (Raichle, 2015; Sheline et al., 2009). The central executive network, with the core regions being the dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex, frontal eye fields, and (partly) the dorsomedial prefrontal cortex, is mostly active during higher cognitive processing and has been linked with a wide variety of cognitive functions (Menon, 2011; Seeley et al., 2007; Sheline et al., 2009). As can be seen, many regions commonly identified in the psychosocial stress response are part of one of these three networks.

Increased connectivity in the salience network has been found both during and after stress induction (Hermans et al., 2011; Van Marle et al., 2010), and has been linked with increased levels of both cortisol and negative affect (Hermans et al., 2011). Increased salience network connectivity has been proposed to reflect an increased attention towards salient stimuli in either the internal or external environment (W. Li et al., 2014; Marle et al., 2009; Menon, 2011). Increased activation is found in most stress paradigms with one exception: the MIST. Both increased and decreased activity and connectivity is found in this paradigm (van Oort et al., 2017). The underlying reason for this inconsistency that is proposed is similar to that of the previous section; the co-occurrence of additional stressors not related to social interactions (van Oort et al., 2017).

The DMN is mostly more active during the stress response (van Oort et al., 2017) and increased connectivity is also found during the recovery phase (Vaisvaser et al., 2013). This result is initially counter-intuitive, given that the DMN is a task-negative network and mostly active during rest (Raichle, 2015). An explanation of this might be that psychosocial stressors that induce negative feelings regarding the self and threaten the social status of the individual (i.e., ostracism or SET; Baumeister & Leary, 1995; Dickerson, 2008; Williams, 2007), result in increased self-reflective thoughts during and after stressor exposure (Muscatell et al., 2015; van Oort et al., 2017). This increased DMN connectivity and activity due to psychosocial stress might explain the influence of psychosocial stress on the development and progression of depression, as it has been linked with maladaptive rumination (Hamilton et al., 2011). Of note here is that significant variability is present again, and similarly to inconsistent changes in the salience network, the presence of co-occuring stimuli such as higher-order cognitive tasks,

rewards, or pain in some stressor paradigms is again proposed as a possible reason for the prevailing variability (van Oort et al., 2017).

Changes in the central executive network are more modest, and increases in CEN are mostly found in stress paradigms that employ cognitive tasks (van Oort et al., 2017). This dissociation was further complicated as some studies employed more difficult tasks in the stress condition than in the control condition, making it difficult to assign neural changes specifically to the stressors (Weerda et al., 2010).

Taken together, FC results highlight the central role of the amygdala in the stress response. The many connections that are influenced due to the presence of a stressor as well as the multitude of studies identifying dysfunctional amygdala connectivity with an array of brain regions in several psychopathologies cement the importance of this region in stress research. Aside from this, three networks: the salience, default mode, and central executive network are heavily implicated in the psychosocial stress response (van Oort et al., 2017). The main conclusions that can be drawn is an increased activity and connectivity in the salience network, likely reflecting the increased attention towards the stressors, and increased activity in the default mode network, possible reflecting processes related to self-referential thoughts. One critical note should be made here: most articles included in the review of van Oort and colleagues (2017) reported activity changes, and only a small percentage directly investigated functional connectivity. This limits the conclusions that can be drawn regarding the involvement of these networks, as activity changes of one region does not necessarily indicate changes in functional connectivity in these networks.

2.2.3.4.3. Current gaps in the literature

Considering the above summary of fMRI results, two limitations can be identified. First is the fact that conclusions regarding the neural psychosocial stress response are often complicated by the co-occurrence of other, non-psychosocial stressors (van Oort et al., 2017). Second is that different stress paradigms evoke surprisingly distinct neural responses, further complicating our understanding of how psychosocial stress affects neural communication (Muscatell et al., 2021). Both limitations are further exacerbated by the disadvantages of fMRI mentioned in section 2.2.3.3., as different neural mechanisms likely result in similar increased or decreased BOLD response patterns.

These limitations specifically are kept in mind in the experimental studies of this dissertation. In chapter 4, SET is induced in participants while co-occuring stressors are kept constant as best as possible, therefore isolating the neural activity related to increased SET exposure and evaluating whether several EEG measures are sensitive to detect purely psychosocial stressors. In chapter 5, a within-subjects design is employed where participants are exposed to two different stressor paradigms (Cyberball and MIST) on different days, thus investigating how different stress paradigms induce similar or dissimilar neural activity. In order to employ the fMRI results as best as possible, ESI is employed so that individual regions that have been identified and described in the previous sections can be investigated, thus potentially bridging the current gap between the fMRI and EEG literature concerning the neural psychosocial stress response.

2.2.4. Electroencephalography

EEG is the main imaging modality employed in this dissertation, so this imaging technique will be explained in most detail. First the origin of the EEG signal is discussed, followed by how EEG is captured and preprocessed. Subsequently, a short summary is provided of the main frequency bands in the EEG signal and their hypothesized role in neural functioning. Afterwards, the various steps in electrical source imaging are explained, followed by the three main analysis techniques that are employed in the following chapters: event-related potentials (ERPs), spectral power, and functional connectivity. The section is ends with a summary of the advantages and disadvantages of EEG.

2.2.4.1. Origin of the EEG signal

The following section is based upon the following works: Cohen, 2014, 2017; Da Silva, 2022; Jackson & Bolger, 2014; van Mierlo, 2013.

EEG signals are obtained by placing electrodes on the scalp of an individual and measuring small potential differences between the electrodes and a reference electrode, and thus reflect changes in electrical charges that present themselves at the scalp. Electrical field changes in the brain arise from membrane potential changes due to neural communication. As seen in section 2.2.1.2., the two main sources of electric field changes are action potentials (APs) and postsynaptic potentials (PSPs). APs result in a membrane potential changes of 70-110 mV that last about 0.3 milliseconds (ms) while PSPs change the membrane potential between 0.1 and 10 mV and last between 10 and 20 ms. Potential differences of single neurons are small and will not be detectable by electrodes at the scalp, so only synchronous activity of large neuron populations (order of thousands to millions; Baillet et al., 2001) will result in a detectable deflection. While APs result in larger potential differences, their short duration limits the posibility of enough APs occuring simultaneously and APs thus do not contribute to the EEG signal significantly. While the potential difference of PSPs is smaller, their longer duration makes a summation possible, and therefore its is PSPs, not APs that contribute to the EEG signal (Baillet et al., 2001). The necessary summation of PSPs however imposes limitations on the type of neuron, and type of activity that will result in a measurable signal. Only large enough neuron populations that exhibit the same (or very similar) excitatory or inhibitory activity will result in a sufficient amount of PSPs that can be summed. Additionally, the orientation of the dendrites of these neurons (where PSPs occur) should be spatially aligned with each other so

that the PSPs of individual neurons amplify, not weaken, one another (Baillet et al., 2001; Jackson & Bolger, 2014).

A specific neuron type, the *pyramidal neuron*, has been identified that can exhibit both characteristics (Avitan et al., 2009). Organized in cortical collumns that lie perpendicular to the cortical surface (see Figure 10A) and thus spatially aligned, it is believed that large populations of pyramidal neurons located near the scalp are the main, though not exclusive, source of the EEG signal (Jackson & Bolger, 2014).

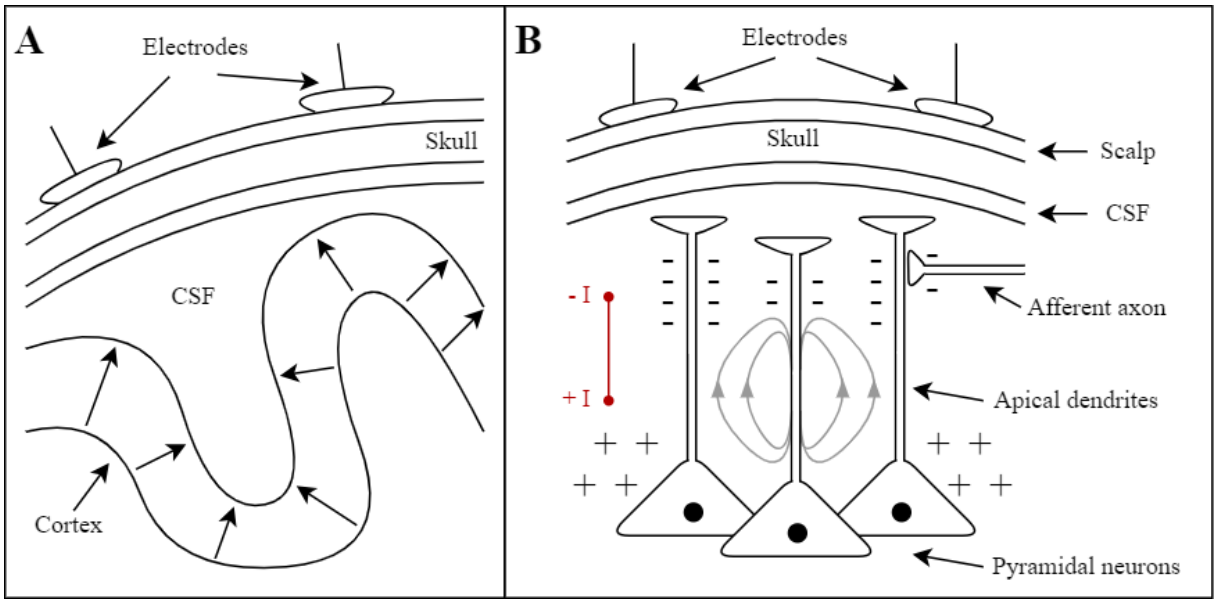

Figure 10: Visualization of the locations of the pyramidal neuron assemblies and cellular mechanisms responsible for the EEG signal. **A)** Orientation of pyramidal assemblies (shown by black arrows) as a function of cortical folding. **B)** Representation of the origin of the EEG signal due to excitation of the apical dendrites of pyramidal neurons. Charge differences are shown by + or -. Simplified current flows are shown by gray arrow lines. The representative current dipole is shown in red with -I being the current sink and +I being the current source. **Note:** this figure is adapted from (Jackson & Bolger, 2014; van Mierlo, 2013).

When excited by afferent axons of presynaptic neurons, the exctracellular fluid near the apycal dendrites becomes more negative compared to the soma of the pyramidal neurons (see Figure 10B). This situation can be considered as a current dipole (i.e., a pair of separated electric charges) where the positive charge is named the source and the negative source the sink (see Figure 10B), and it is the sum of these individual charges that the EEG electrodes will measure (Jackson & Bolger, 2014). Several considerations are needed here. Firstly, inhibition of the apycal dendrites will result in a dipole of opposite direction (considering Figure 10B, the source and sink would switch places). Secondly, positive or negative charges do not indicate cell activation or inhibition as both processes result in dipoles. Thirdly, the orientation of pyramidal cell assemblies are perpendicular to the cortex surface, but are not always perpendicular to the skull and scalp surface (see Figure 10A), therefore only pyramidal assemblies that are either

perpendicular or radial to the scalp surface will contribute significantly to the EEG signal (Jackson & Bolger, 2014) as the distance between the positive and negative charges, and the electrode itself, is maximal in these configurations.

The dipoles are located in the cortex, and between the cortex and the scalp (where the electrodes are located, see Figure 10A and B) several tissues are located, being cerebrospinal fluid (CSF), the meninges, and the skull. This means that the charges need to "travel" (i.e., a cascade of repelling ion groups from the inital charges to the electrodes) through these tissues to arrive at the electrode, which is called *volume conduction*. Due to the different conductivities of these tissue types the signal will attenuate, resulting in signals at the scalp in the range of microvolts (μV), several order of magnitude lower than the initial potential differences. Aside from attenuating, the signal will also not directly travel to the nearest electrode, but instead spreads through the tissue which results in multiple electrodes measuring the same source. Of note here is that this is a simplified description of the generation and measurement of EEG, the interested reader is referred to the following articles and books: Cohen, 2014, 2017; Jackson & Bolger, 2014.

2.2.4.2. Measuring the EEG signal

As stated above, EEG is most commonly measured by placing electrodes on the scalp of an individual. The electrodes will measure charges at the specific place on the scalp where they are located and will do so multiple times each second. The amount of times that the potential at an electrode is measured within a single second is called the *sampling frequency* or *sampling rate*, and has the unit Hertz (Hz). Commonly employed sampling frequencies are 512 Hz (i.e., 512 samples per second) or 1024 Hz. Of note here is that EEG has a high temporal resolution compared to fMRI, which has a temporal resolution of up to 1 Hz (Finn et al., 2023).

In order to compare the EEG of multiple individuals, the electrodes are placed at standard locations on the scalp that are defined by several anatomical landmarks, with the most commonly employed placement scheme being the 10-20 system (Klem, 1999). The 10-20 system uses four anatomical landmarks for the positioning of the electrodes: the nasion (i.e., depression between the eyes above the nose), the inion (i.e., lowest point of the back of the skull, often exhibiting a distinct protuberance), and the pre-auricular points (i.e., the point right in front of the ear). Additionally, each electrode location is indicated by a letter (or letters) and a number. The letters indicate the area of the brain where the electrode is located above: Fp (prefrontal), F (frontal), C (central), T (temporal), P (parietal), and O (Occipital). One additional

letter can be present: Z, which indictates that the electrode is located on the midline saggital plane (i.e., these electrodes lie on the line connecting the nasion, uppermost point of the head, and inion). The numbers indicate the deviation from the midline, with higher numbers indicating further deviations. Odd numbers indicate that the electrode is located on the left side of the head, and even numbers define the right side. From these rules, it can be deducted that F3 is located on the left frontal lobe, and that it is located nearer to the midline than F5 (Klem, 1999).

As previously mentioned, the potentials at the scalp are minimal so the impedance between the electrode and scalp should be as low as possible. This is done by either applying a conducting gel between the scalp and electrode or a saline solution to the sponge surrounding the electrode (called wet electrodes). Dry electrodes that do not require any conducting liquid can also be used (Di Flumeri et al., 2019). The required impedance depends on the type of amplifier that is employed, with low-impedance systems normally requiring impedances below 5 kilo ohm (kΩ) and high-impedance systems requiring impedances below 50 kΩ. The measured signal at the electrodes is subsequently amplified which is done to *1)* maximize the signal-to-noise ratio (SNR) of the measured voltage and *2)* maximize the measured signal relative to the electrical noise that is introduced later in the electrical circuits (Jackson & Bolger, 2014). Once amplified, the signal is saved and can subsequently be preprocessed and analyzed for its intented purpose.

2.2.4.3. Preprocessing the EEG signal

The quality of the saved EEG signal is dependent on the obtained impedance of the electrodes and quality of the recording device, and therefore correct application of the EEG electrodes is critical for conducting high-quality EEG research. Nevertheless, the collected EEG data will contain artifacts from either other physiological processes (e.g., heartbeat, eye-movement, muscle contractions) or electrical interferences (e.g., net line noise). Therefore, the collected EEG data does not only contain neural activity but also artifacts from unrelated physiological processes and electrical interferences. Preprocessing EEG data can thus be seen as multiple processes that try to remove the physiological and electrical artifacts as best as possible, without removing neural activity or leaving it intact as best as possible.

There is no agreed upon standard preprocessing pipeline for EEG data, and the steps taken as well as the order in which they are taken depends both on the present artifacts and EEG data quality, as well as the intented purpose of the EEG data (Robbins et al., 2020). Discussing all possible analyses falls outside of the scope of this dissertation, but the steps taken in the studies presented in chapter 4 and 5 will be discussed shortly. These artifacts will be discussed with respect to whether they are removed in the time or frequency domain.

2.2.4.3.1. Artifacts in the frequency domain

As stated before, EEG is sampled at a high sampling frequency (up to 1 or 2 kHz). This makes it possible to transform the signal into the frequency domain, which is most commonly done by using the *fourier transform*, although the wavelet transform is also sometimes used (Yang et al., 2013). The fourier transform, in simple terms, models the EEG signal as a sum of sine waves that each have a specific amplitude, phase, and frequency. When the signal is measured continuously (i.e., with infinite sampling frequency), the fourier transform can model a signal perfectly, but when finite sampling frequencies are employed, the highest sine wave that can be considered has a frequency that is half of the sampling frequency due to Nyquist theorem. Therefore, an EEG signal sampled at 1 kHz can only be approximated by sine waves up to 500 Hz and can thus not be reconstructed perfectly. The discrete (i.e., not continuous) fourier transform is presented in formula 3, where *X(k)* is the signal as a function of frequency *k*, x_n is the sample at timepoint *n*, and $\varepsilon^{-i2\pi kn/N}$ describes the sine wave in complex notation as a function of frequency *k*, current sample *n* and tot total amount of samples *N*. $\varepsilon^{-i2\pi k}$ can thus be understood as the complex notation of a sine wave of frequency *k*. Taken together, the fourier transform transforms an EEG signal that is described as *voltage value/sample* into a signal that is described as *amplitude/frequency*, and is commonly visualized using a spectrogram.

$$X(k) = \sum_{n=0}^{N-1} x_n . \varepsilon^{-i2\pi kn/N} \quad (3)$$

The fourier transform allows the removal of three artifacts that occur at very specific frequencies: stationary and low frequency drifts, net line noise, and high frequency electrical noise. Stationary and low frequency drifts refer to either the offset of the EEG signal (stationary) from zero, and very slow drifts introduced by the electrical systems. Net line noise refers to the electrical fields generated by the electrical cables in the vicinity of the EEG recording device, which oscillates at 50Hz in Europe and 60 Hz in America (Jackson & Bolger, 2014). High frequency electrical noise refers to noise at high frequencies where no neural activity is assumed to be present. These artifacts can be removed by filtering the signal in the frequency domain.

Two filters are employed for this: a bandpass filter, defined by a the lowest and highest frequency that needs to be included in the signal while removing other frequencies, and a Notch filter, defined by the specific frequency that needs to be removed. Commonly employed bandpass frequencies are 0.5 Hertz (thus removing stationary and slow frequency drifts) and 40-50 Hz (thus removing high frequency electrical noise) and depending on the location, 50 or 60 Hz is used for the Notch filter. Figure 11A shows an EEG signal containing these artifacts, Figure 11B shows the spectrogram of this EEG signal, Figure 11C shows the EEG signal after filtering, and Figure 11D shows the spectrogram of the filtered EEG signal.

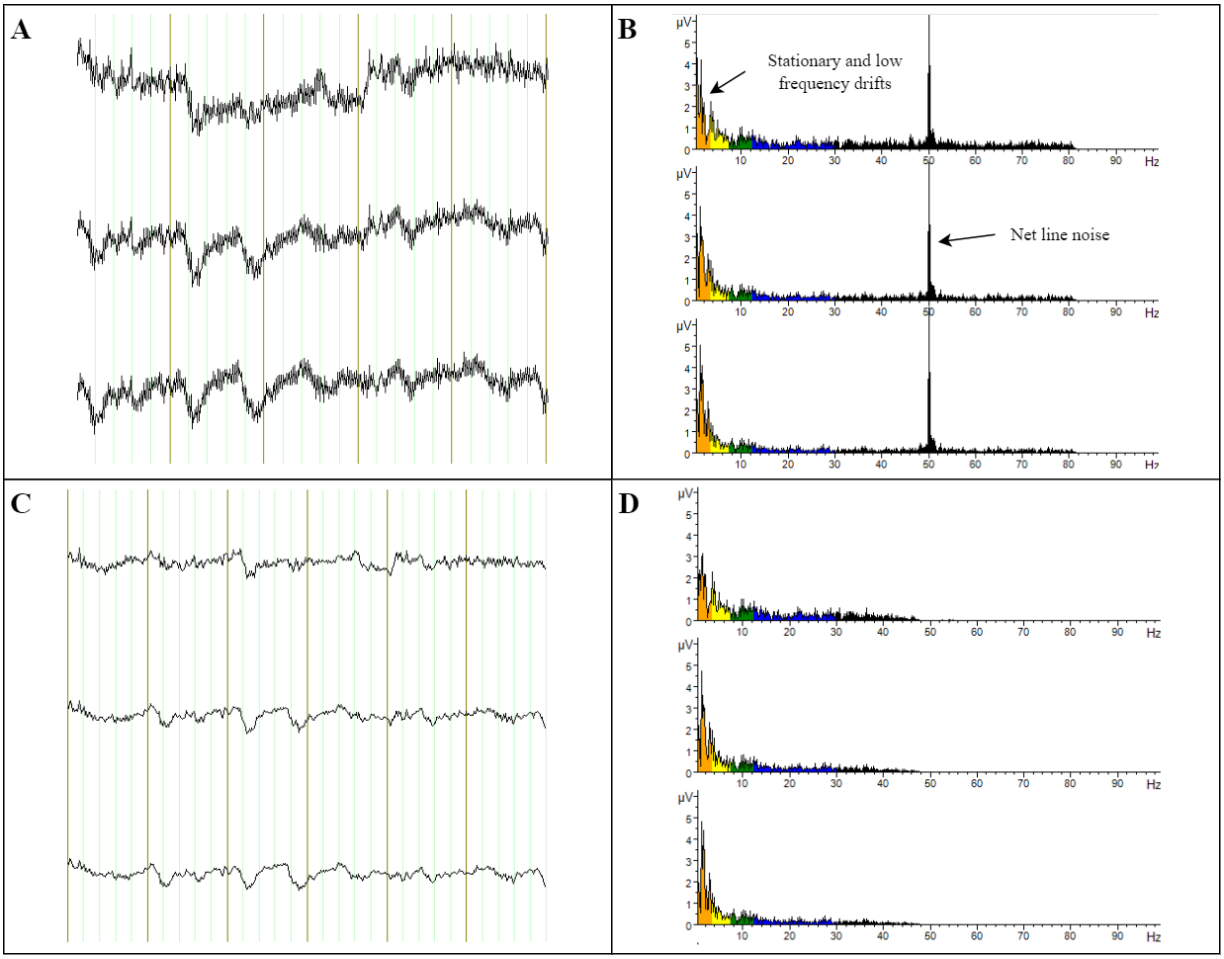

Figure 11: Visualization of EEG data with and without stationary and low frequency drifts and netline noise. **A)** EEG data with artifacts. **B)** Spectrogram of the EEG data with artifacts. **C)** EEG data without artifacts. **D)** Spectrogram of the EEG data without artifacts. **Note:** This figure was made using the Brainvision Analyzer software.

2.2.4.3.2. Artifacts in the time domain

Filtering of the EEG signal is commonly conducted first as it allows a clearer visual inspection of the data. Subsequent artifacts are mainly identified in the time domain (although they have a frequency representation) and are thus mostly removed in the time domain. These artifacts are: bad channels, ocular, muscle, and cardiogenic artifacts. Bad channels are EEG electrodes that either do not record correctly, or are disconnected from the scalp. These channels thus are not able to record neural activity and are consequently of no value in further analysis. They are deleted and if possible, interpolated (i.e., reconstructed from nearby channels under the assumption that these channels have detected highly similar potential changes due to volume conduction). Ocular artifacts are potential changes due to eye movements which result in deflections in the EEG signal, most prominent at frontal electrodes due to the volume conduction (see Figure 12A). Cardiogenic artifacts are a result of heart contractions. The generated potentials from heart contractions is much bigger than the neural potentials and thus can sometimes be measured by the electrodes due to volume conduction. Both artifacts are often removed through *independent component analysis* (ICA; Li et al., 2006). A full explanation of this algorithm is beyond the scope of this dissertation, but briefly stated: ICA deconstructs the signal into a set of statistically independent signals and relies on the assumption that the recorded signal is a linear combination of said statistically independent signals (Y. Li et al., 2006). ICA decomposition is limited by the amount of signals that it can use and thus can only deconstruct the signals into an equal amount of independent components. Therefore, to obtain the best seperation possible, all EEG channels are used for this preprocessing step.

ICA is capable of separating the signals introduced by eye movement and cardiac contractions as the processes occur independently of neural activity. While eye movement are clearly visible in the EEG signal (see Figure 12A), cardiac artifacts are less easily identified and can only be seen when looking at the components themselves. ICA can be conducted either automatically, whereby specific rules define when a component is considered ocular or cardiac (based on its time course, topographic distribution, and statistical properties, employed in chapter 5), or semi-automatic, whereby the researcher visually inspects the components and selects the components that contain the aforementioned artifact (employed in chapter 4). These artifacts are subsequently removed by reconstructing the EEG signal but excluding the components that are deemed to contain artifacts.

Muscle artifacts can be caused by a variety of processes including but not limited to movement (Figure 12C), grinding of the teeth (Figure 12B), swallowing, or frowning (Jiang et al., 2019). While these processes can be considered independent from neural activity, they can not be removed with ICA as they are less consistent in time or origin than cardiac or ocular artifacts, resulting in inconsistent statistical properties. Muscle artifacts are however detectable due to several characteristics, of which the high amplitude and sudden change are the most common. These artifacts can thus be detected by defining an allowed range of the signal in a predefined time window (min-max criterium), a sudden jump in the signal (gradient criterium). A third criterium can also be employed, the low activity criterium, which can detect temporary "flatlines" in the EEG signal due to temporary electrode disconnection. While these artifacts can be detected, their specific presentation in the EEG signal makes it impossible to remove them. Therefore they are tagged as bad, and data containing artifacts are removed before analysis.

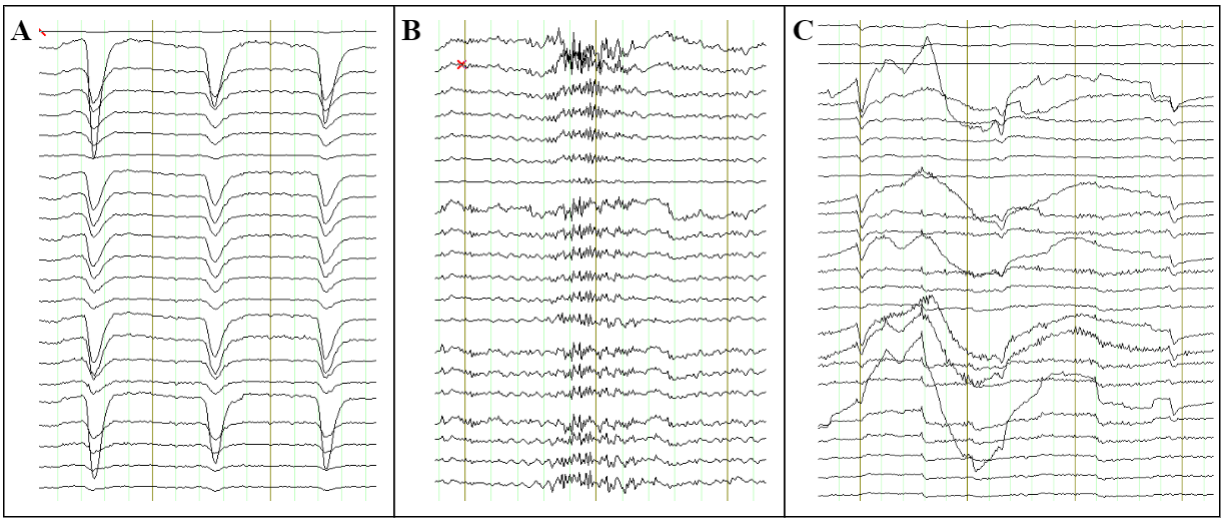

Figure 12: Visualization of common EEG artifacts. **A)** eye movement artifact. **B)** Grinding/biting artifact. **C)** Movement artifact. **Note:** This figure was made using the Brainvision Analyzer software.

2.2.4.3.3. Rereferencing

A final step in the preprocessing process is the rereferencing of the EEG data. As mentioned above, EEG signals are defined as voltages and therefore reflect potential differences. The EEG signal of an electrode is thus not the potential at that electrode, but the difference between the potential at that electrode and a reference electrode, which was Cz in chapter 4 and 5. Considering the location of the electrodes, it is likely that electrodes near the reference electrode capture highly similar neural activity, resulting in small potential differences and thus small deflections in the EEG signal. Electrodes located further from the reference likely capture more different neural activity, resulting in larger described voltages. Given a

single reference electrode, the amplitude of each channel will thus in part be a function of it distance to the reference. This in itself is not an issue when the EEG signal is directly analyzed and all data is analyzed with the same reference, but when electrical source imaging (ESI, see below) is employed, it might lead to incorrect estimates of the source distribution. Therefore, in chapter 4 and 5 the "average reference" is employed, which simply averages all channels and subsequently subtracts this signal from each individual channel. As with other preprocessing steps, each reference option has advantages and disadvantages and no reference is generally considered the best, but reference choice has a significant impact on subsequent analysis results (Chella et al., 2016; Trujillo et al., 2017; Yao et al., 2019).

2.2.4.4. Contents of the EEG signal

The first description of EEG stems from 1929 where the first scalp recording by Hans Berger in 1924 is presented. Hans Berger identifies two waveforms, an alpha (i.e., the first letter of the alphabet) and beta (i.e., the second letter) wave (Berger, 1929). Since 1929, additional prominent waves in the human EEG have been identified and based on the frequency range in which they occur and amplitude they display, five common frequency bands have been defined: the *delta*, *theta*, *alpha*, *beta*, and *gamma* band. It is believed that this oscillatory behavior arises from cyclic activation and deactivation of pyramidal neuron populations, and that each frequency band represents specific cognitive functions and working mechanisms of the brain (Cohen, 2017).

The delta band refers to oscillations occuring at a frequency of less than 4 Hz. Delta waves are prominent in the EEG of sleeping individuals, is present in early developmental stages, and increases during panic or sustained pain. In cognitive neuroscience, delta waves have been linked with attention and salience detection, and it has been proposed that these slow waves reflect the integration of neural activity with homeostatic processes (Knyazev, 2012). The theta band refers to oscillatory activity between 4 and 8 Hz. Theta waves have been linked with cognition and memory specific processes, sensory and motor processing, and emotional consolidation during sleep (Karakaş, 2020; Klimesch, 1999; Nigbur et al., 2011; Nishida et al., 2009). The most prominent oscillations lie between 8 and 12/13 Hz, which is considered the alpha band. Alpha activity is believed to reflect inhibitory mechanisms in the brain where increased alpha activity indicates decreased cortical activity (Allen et al., 2004; Bonnefond & Jensen, 2012; Händel et al., 2011; Jensen & Mazaheri, 2010; Mathewson et al., 2011). The beta band, defined between 13 and 30 Hz, has been proposed to reflect mechanisms related to attention as well as sustaining sensorimotor and cognitive states (Engel & Fries, 2010; Miller,

2007; von Stein & Sarnthein, 2000; Wróbel, 2000). The gamma band, reflecting oscillations above 30 Hz, is proposed to reflect cognitive processes related to memory matching, object binding and is involved in early sensory processing (C. S. Herrmann et al., 2010; Miltner et al., 1999). Several of the aforementioned frequency ranges have also been subdivided further, as more specific ranges might reflect more specific neural mechanisms.

Aside from these five commonly investigated bands, several other frequency ranges have been defined and investigated. Important additional frequency bands are the *mu* band, *sigma* band and *high-frequency* neural activity. The mu band encompasses roughly the same frequencies as the alpha band, but originates from the motor cortex while alpha rhythms are more prominent over the visual cortex. Activity in the mu band has been linked with the mirror neuron system in humans whereby mu suppression (similarly to decreased alpha activity reflecting increased cortical activity) occurs both during observing and executing actions (Fox et al., 2016). The mu band is addtionally investigated throughout the developmental stages of humans to obtain insights into how social learning and imitation develops in children (Cuevas et al., 2014). Considering that imitation is impaired in individuals with autism spectrum disorder (ASD), alterations in mu suppression in this group of individuals has also been researched (Bernier et al., 2007). The sigma band, mostly investigated in relation to different sleep stages, considers frequencies between 12 and 15 Hz and is thus a subsection of the beta band (Ferri et al., 2001 ; Spiegelhalder et al., 2012). Finally, high-frequency activity, ranging from 50 to hundreds of Hz, has also been investigated using EEG. Activity in these ranges has mostly been investigated in relation to epileptic spikes and seizures (Arroyo & Uematsu, 1992; Urrestarazu et al., 2006). Aside from oscillatory, periodic activity, the EEG signal also contains aperiodic components, called bursts. These have been observed in early life (Schaworonkow & Voytek, 2021), but are not as often researched yet (Donoghue et al., 2020).

One critical reflection should be made here. Upon first measuring the alpha wave, Hans Berger ponders on what exactly it reflects (Berger, 1929). Almost one century later, this question is still unanswered.

2.2.4.5. Electrical Source imaging

Electrical source imaging (ESI) refers to the mathematical operations that estimate the most likely source distribution in the brain that resulted in the EEG data captured at the scalp (Michel & Brunet, 2019). ESI consists of two steps : solving the *forward* and *inverse problem.*

2.2.4.5.1. The forward problem

The forward problem estimates how a given source or source distribution in the brain impacts the electrodes at the scalp (see Figure 13A) and results in the construction of the *lead field matrix* (Michel & Brunet, 2019). In order to do this, first a *head model* is constructed. A head model is, as it name gives away, a digital reconstruction of the head built up from different tissue types and thus provides a model for the expected volume conduction that will occur. Head models can be constructed in a variety of ways with the most simple head models being built up of concentric spheres (i.e., spherical head models), each representing a different tissue type (Cuffin, 1996). Technological advances in ESI have however significantly improved head models, and currently most head models are reconstructed realistically from MRI images (see Figure 13B) and the best construction of head models is obtained when high-quality T1 and T2 images are available (Cuffin, 1996). From MRI images, tissue types can be identified through segmentation, which can be understood as the extraction of separate images that each represent a single tissue, with commonly extracted tissue types being the skin, skull, white matter, gray matter, cerebrospinal fluid, and air, from an MRI image. Of importance is that the separate images should be nonoverlapping (i.e., a single location in space can only attributed to a single tissue type) and that the segmented images are meaningful (e.g., the skull is a continuous structure without gaps) (Despotović et al., 2015). When available, individual MRI scans should be employed for head model generation as anatomical differences between individuals such as skull thickness or cortex folding will influence the measured potentials at the scalp (Michel & Brunet, 2019). When no individual MRI images are present however, a *template* MRI image can be employed. A complete description of this process falls outside the scope of this dissertation, but the interested reader is reffered to the following articles: Despotović et al., 2015; Michel & Brunet, 2019.

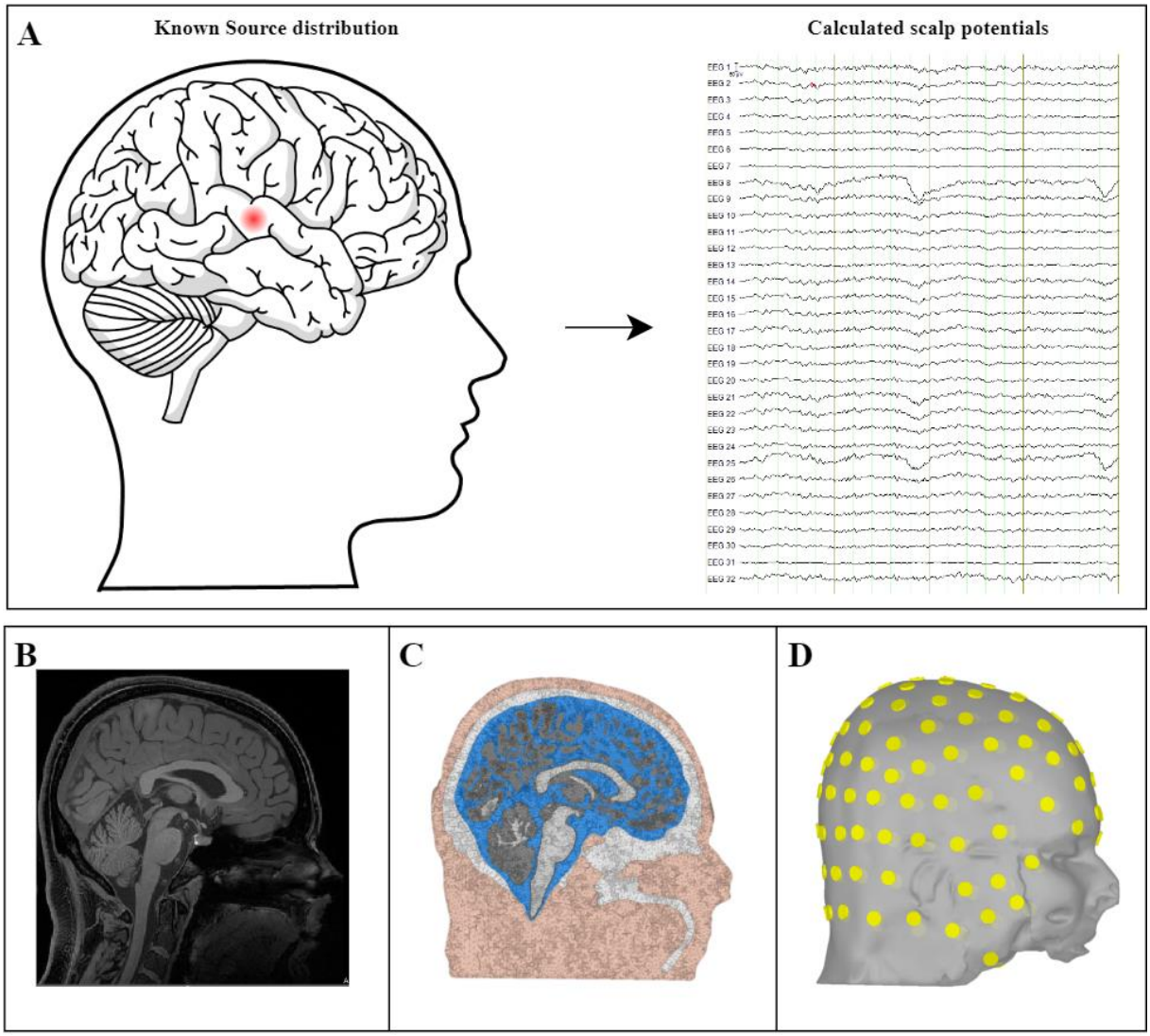

Figure 13: Visualization of the forward problem and the steps taken to obtain the lead field matrix. **A)** the basic premise of the forward problem: given a known source distribution (e.g., the red blurred dot on the right superior temporal gyrus), how does this affect the potentials of the electrodes at the scalp? **B)** An MRI image used to generate the head model. **C)** A five-layer FEM head model. **D)** A visualization of the electrodes placed on the scalp of the head model based on anatomical landmarks. **Note:** This figure employs a visualization obtained from Freepik, subfigures B, C, and D were obtained from BrainStorm.

After segmentation, potential sources of neural activity need to be defined. These potential sources are modeled as a dipole as it represents charge differences between the apical dendrites of synchronously active pyramidal neurons and their somas (see section 2.1.4.1.), and this approximation has been validated experimentally (De Munck et al., 1988). Dipoles are defined by six parameters: the position $R = [x\ y\ z]$, orientation θ and Φ (defined as angles), and intensity I (i.e., amplitude). It is impossible to know the real location of these sources, but an acceptable assumption is that sources of neural activity can only be present in gray matter (Michel & Brunet, 2019).

Three source models can be defined: *single dipole*, *multiple dipole*, and *distributed source* models. In single dipole models, a single dipole is defined in the gray matter. The advantage of this approach is that the solution can be obtained analytically and requires no estimation as the number of unknowns (i.e., the orientation and intensity of the dipole) is lower than the amount of electrodes. This however requires the a priori placement of the dipole, possibly inducing biases and not representing normal cortical activity (Hara et al., 1999). This approach can be considered however when activity in a single brain region is heavily suspected, sometimes applicable in epilepsy research for the identification of the seizure onset zone (SOZ; Thornton et al., 2011). Multiple dipole moment place multiple dipoles in the brain, but still ensure that the numbers of unknowns is smaller than the number of known variables (i.e., the amount of electrodes). Similar concerns however are present as the single dipole models. The final possible source model is the distributed source model. This model does not assume an a priori location of possible neural sources, and instead places sources at equidistant locations throughout the gray matter. In chapter 4 and 5 a distance of 5mm between sources was chosen. This approach results in the most realistic modeling of neural activity, but results in more unknown (i.e., descriptions of dipoles) than known (i.e., electrodes) variables and thus requires estimations to obtain a solution as the problem is ill-posed (Bakushinsky & Goncharsky, 2012). The number of unknowns can be reduced by restricting the orientation of the dipoles to be perpendicular to the cortical surface which can be estimated from the segmented image, but the problem remains ill-posed. After defining the possible neural sources, the electrodes are co-registered to the head model, most commonly done through visual inspection using the nasion, inion, and pre-auricular points as landmarks (see Figure 13D).

The forward problem is subsequently solved. As mentioned before, this solution will result in a lead field matrix which describes the relation between activity of the neural sources and measured potentials of the electrodes (Wolters et al., 2004). The lead field matrix can be obtained using formula 4, where V represents the potentials of N electrodes ($V = [V(R_1)\ V(R_2)\ \dots\ V(R_N)]$), L represents the lead field matrix, R_d describes the position of a single dipole ($R_d = [x_d\ y_d\ z_d]$), and d descripes the dipole moment of the considered dipole, defined as the product of the intensity I and the displacement vector s ($d = I.s = [dx\ dy\ dz]$).

$$V = L(R_d)d \tag{4}$$

Although formula 4 might look simple, obtaining a solution is nontrivial. Three techniques can be employed: the *boundary element method* (BEM; Katsikadelis, 2002, 2016), the *finite element method* (FEM; Dhatt et al., 2012; S. S. Rao, 2017), and the *finite difference method* (FDM; Mitchell & Griffiths, 1980). A full explanation falls outside the scope of the dissertation, but briefly stated : BEM defines the different tissue types as surfaces (i.e., boundaries) modeled by small triangles and requires tissue types to be homogeneous (i.e., have the same conductivity). Subsequently the potentials at these boundaries are iteratively calculated to obtain the lead field matrix. FEM divides the head model in small tetrahedrons, an thus models the brain volumetrically. This allows each tetrahedron to be a different tissue type or have different conductivity, but is computationally more complex and takes longer to compute. FDM divides the brain into a homogeneous voxel grid, but is less commonly employed than BEM of FEM (Cuartas Morales et al., 2019). All methods subsequently solve the Maxwell's equations to obtain the lead field matrix. The interested reader is referred to the aformentioned articles and books.

Taken together, the forward problem results in a lead field matrix that decribes the relation between the sources in the brain and the electrodes at the scalp.

2.2.4.5.2. The inverse problem

The inverse problem refers to the estimation of the source distributions that best explains the data measured at the electrodes using the lead field matrix obtained from the forward solution, as visualized in Figure 14 (Michel & Brunet, 2019). Given that only distributed source models were employed in this dissertation, only this problem will be discussed. For an explanation of the inverse problem regarding single and multiple dipole models, the reader is referred to Michel et al., 2004. The inverse problem of distributed source models ill-posed as more unknown variables are present (i.e., the orientation and intensity of the dipoles) than known variables (i.e., electrodes). The consequence of this is that infinite source distributions can explain the data measured by the electrodes. As a simple example, consider formula 5. This equation contains one known variable, 1, and two unknown variables, x and y. It is obvious that an infinite amount of values of x and y will result in a correct solution.

$$1 = X + Y \tag{5}$$

A researcher however has little interest in infinite possible solutions, but rather requires a single solution that best represents the underlying electrical activity that gave rise to their measured EEG data. Therefore, constraints need to be included during the solution of the

inverse problem, and several have been proposed that vary based on certain assumptions regarding neural activity. A first constraint is that the overal intensity of the considered dipoles should be minimal, thus the solution with the overall lowest activity will be the correct one. This constraint is called *minimum norm estimation* (MNE) and relies on the assumption that the brain optimizes energy usage for neural communication (Hämäläinen & Ilmoniemi, 1994; Michel et al., 2004). This assumption is valid, as neural activity of small localized groups is more realistic than significant activity across the entire brain, but introduces a bias in the result by favoring superficial (i.e., close to the electrodes) solutions. Given that the signal attenuates before reaching the electrodes (see section 2.1.4.1.), activity from dipoles located close to the electrodes will attenuate less than activity from more distant dipoles, so a smaller intensity of these dipoles will result in a potential change at the electrodes that is equal to larger intensities of deeper dipoles. To solve this bias, minimum norm estimates were expanded by including weighting, called *weighted minimum norm estimation* (wMNE), where the distance between the dipole and electrodes is considered in the solution and many approaches have been proposed (Michel et al., 2004). Additional constraints can be introduced by considering additonal aspects of neural communication. One such assumption is that electrical activity is correlated between local neuron groups and is thus "smooth", as significant activity in one group of neurons without some activity in neighbouring neuron groups is unlikely. This constraints is incorporated in *laplacian weighted minimum norm* (LORETA), but has been critisized for resulting in blurred solutions that do not represent realisitc neural activity (Fuchs et al., 1994; Michel et al., 2004). Additional approaches for the inverse problem have also been proposed, such as local autoregressive average or beamformer, but will not be discussed further (see Michel et al., 2004 for more information). In chapter 4 and 5, wMNE was employed.

To understand the inverse problem and its solution, consider EEG data measured at N channels, and a source model with P dipoles located in the gray matter. The question that needs to be solved is finding M, which reflects the intensity of the dipoles, given the measured EEG data. Depending on whether the orientation of the dipoles was contrained (i.e., perpendicular to the cortical surface) or not, the size of M will be either equal to P, or equal $3P$ (as the orientation also needs to be estimated). The mathematical solution to this problem is given in formula 6 (Hämäläinen, 2005). Here R is the source noise covariance matrix, L is the lead field matrix (obtained from the forward problem), λ^2 is the regularization parameter (this incorporates an assumption of the a priori variance of the source currents, large values results in smooth current estimates while small values allow larger current amplitudes and "rougher" source

distributions), C is the sensor noise covariance matrix, and uppercase T defines the transpose of the matrix. The sensor and source noise covariance matrices (i.e., C and R) are dependent on the choice of constraint that is imposed during the solution, thus MNE or wMNE will employ different matrices to obtain the solution (Hämäläinen, 2005). The intensities of the dipoles as a function of time can be obtained using formula 7, where $j(t)$ is the intensity of the dipoles at timepoint t, M is the intensity matrix obtained from fomula 6, and $v(t)$ is the EEG data measured at the electrodes at timepoint t. Solving the inverse problem is nontrivial, but a more in-depth description falls outside of the scope of this dissertation. The interested reader is referred to the aforementioned articles for further information.

$$M = RL^T(LRL^T + \lambda^2 C)^{-1} \quad (6)$$

$$j(t) = M.v(t) \quad (7)$$

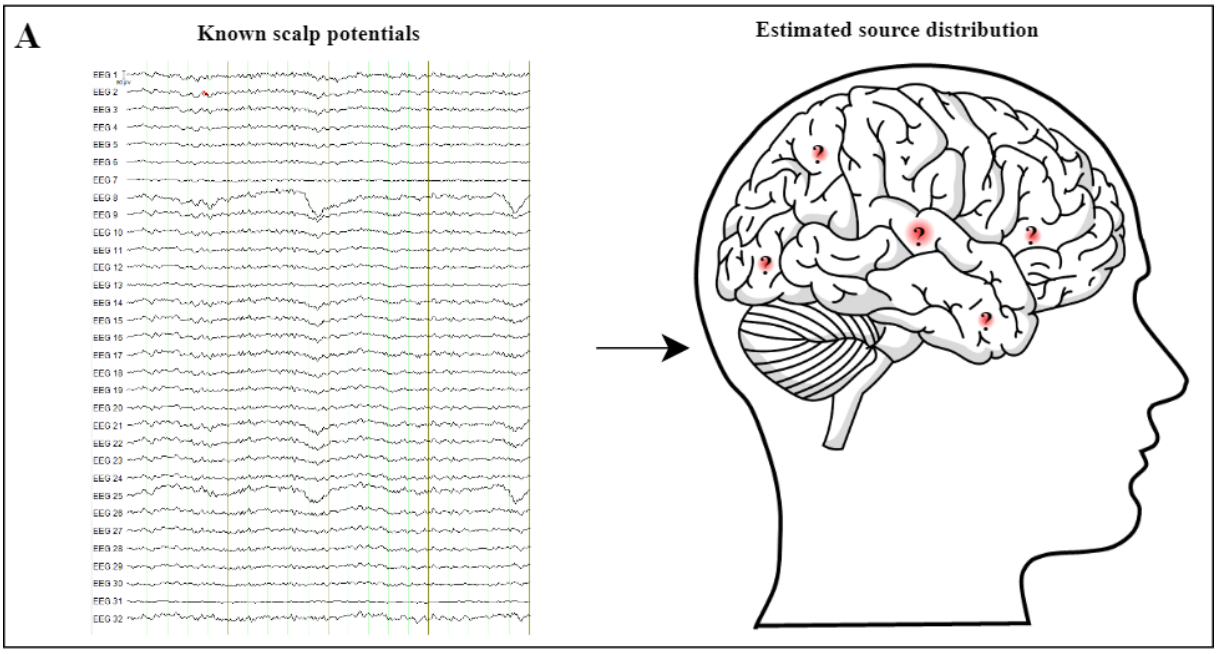

Figure 14: The basic premise of the inverse problem. Given known scalp potentials (obtained through measuring EEG), what is the most likely source distribution that resulted in the measured scalp potentials? **Note:** This figure employs a visualization obtained from Freepik.

The reader likely has noticed that the solution of the inverse problem is an estimate and might wonder what the accuracy of these estimates is. This question is not easy to answer, as it depends on a great variety of factors including but not limited to the choice of head model, employed constraints during the inverse problem, and intented goal of the EEG data or suspected neural mechanism that is responsible for the observed patterns in the EEG signal. Improving the accuracy of ESI is an active field of research, so this paragraph is limited to the discussion of two factors: individual/template head models and number of electrodes. As stated

before, individual MRI scans are favored for ESI, but are often not available due to financial of time constraints. Template MRIs will however not correspond completely with the anatomy of the individual and differences regarding cortical thickness and especially skull thickness, given its low conductivity, will result in decreased accuracy of the final estimation (Cuffin, 1993; Lanfer et al., 2012). Individual head models result in estimate errors below 1 cm, while average head models have estimate errors between 1 and 2 cm, depending on other choices (Valdés-Hernández et al., 2009). The amount of electrodes, often called *electrode density*, also has a significant influence on the final accuracy of ESI where a larger number of electrodes results in better accuracies. A generally accepted minimum amount of electrodes is 64, but sometimes 32 electrodes have been employed for ESI, although the estimated accuracy of this is 3-7 cm (Song et al., 2015; Srinivasan et al., 1998). Higher number of electrodes (i.e., 128 or 256) lead to estimate errors (sometimes) lower than 1 cm, and is thus acceptable for many clinical and research applications (Cuffin, 1996; Song et al., 2015; Stenroos & Hauk, 2013). Two notes are needed here: localizations errors increase with distance from the electrode, making it difficult to obtain accurate estimates of regions located deeper within the brain. Additionally, inaccuracies of ESI estimates are not necessarily consistent across individuals. Comparing multiple ESI results on a group level thus results in a spread of the localization error, possible complicating the interpretation of results on a group level (Song et al., 2015).

While the estimation errors might disencourage researchers to employ ESI, it should be noted that these are often obtained from simulation studies where activity is modeled at a single dipole and the estimate error is computed compared to this dipole. This approach is correct, but one should consider how relevant these errors are regarding their research questions. While extremely important in certain areas of research (e.g., the identification of the seizure onset zone, the region in the brain responsible for seizures in patients with epilepsy; Staljanssens et al., 2017), many field evaluate the brain on a broader scale and consider lobes or regions that encompass multiple cubic centimeters. While estimate errors are also present in these studies, their relative influence is less as the size of the region of interest (ROI) is often larger than the likely errors due to the estimation of ESI. Of special interest here are brain atlasses, where a template brain is divided into several regions that are either anatomically (i.e., considering different gyri or lobes) or functionally (i.e., considering differences in activity) distinct (A. C. Evans et al., 2012). This allows researchers to translate source distributions obtained from ESI into time series of well known ROIs for subsequent analyses by either averaging the activity of each dipole that is asigned to a specific ROI or extracting the first principal component through

principal component analysis (PCA). Atlasses are often accompagnied with a template MRI, and are thus an excellent tool for EEG researchers that have no individual MRI images of their participants. One such atlas is the *USCBrain* atlas, which provides a division of 130 regions in total, as each hemisphere is divided into 65 ROIs, see Figure 15 (Joshi et al., 2022). This atlas is employed in chapter 4 and 5. While this approach might mitigate some of the issues related to the limited spatial resolution of EEG, it is by no means a guarantee that ESI localization errors and spreads are not capable of influencing the final results, and researchers should thus always consider their results with caution. Taken together, ESI is a technique by which EEG data captured at the scalp can be transformed into source distributions, making it possible to investigate the likely neural generators of the EEG data.

Of importance for this dissertation is the fact that ESI allows the researcher to employ fMRI results for the identification of brain regions that they want to investigate, which allows them to combine the knowledge regarding the neural psychosocial stress response present in the vast fMRI literature concerning the subject with the higher temporal resolution inherent to EEG. ESI thus has the potential to bridge the current gap between the fMRI and EEG literature.

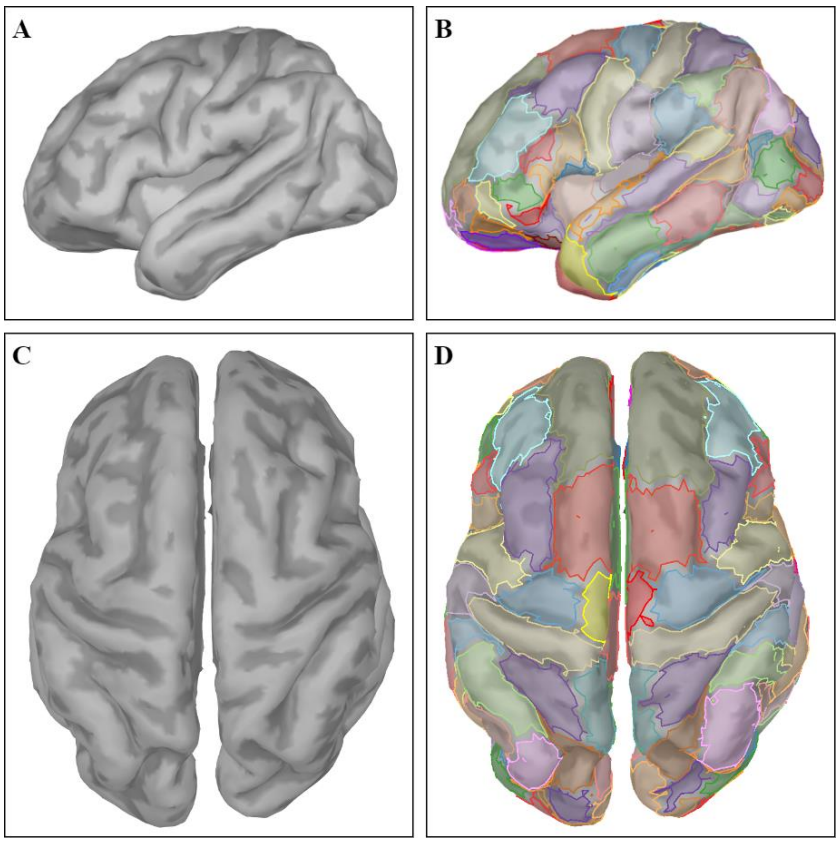

Figure 15: Visualization of the USCBrain atlas parcellation on a smoothed cortical surface. **A)** Left side view of the cortical surface without ROIs. **B)** Left side view of the cortical surface with ROIs. **C)** Top side view of the cortical surface without ROIs. **D)** Top side view of the cortical surface with ROIs. **Note:** These figures were obtained from BrainStorm.

2.2.4.6. Analysis of the EEG signal

In clincical care, EEG is sometimes interpreted visually during sleep or for epilepsy diagnosis (Tatum IV, 2021). In research EEG is more commonly analyzed quantitatively which is sometimes called quantitative EEG (qEEG). qEEG can be understood as the quantification of EEG characteristics and is thus best understood as a broad term describing a multitude of EEG analysis techniques, and the meaning of the acronym is dependent on the individual or group using it. A multitude of analysis techniques have been developed and proposed, and a full explanation of all of them falls outside of the scope of this dissertation. Here we will discuss the three main analysis techniques that are employed or investigated throughout this dissertation: event-related potential (ERP) analysis, spectral power analysis, and functional connectivity (FC) analysis.

2.2.4.6.1. Event-related potentials

Event-related potentials are small deflections in the EEG signal following shortly after a stimulus is presented and are believed to reflect the processing of said stimulus (Luck, 2014). The occurrence of ERPs can be as short as 100 ms post-stimulus, showing the advantage of the high spatial resolution of EEG. ERPs are commonly employed for the investigation of specfic sensory systems such as the visual or auditory system, but are also employed for the investigation of more cognitive and emotionally complex phenomena (Luck, 2014). A full discussion of the usage and insights regarding ERP research falls outside of the scope of this dissertation, but the reader is reffered to the following book, specifically chapter 3: Luck, 2014.

A first consideration regarding ERPs is that the voltage fluctuations are very small (i.e., low SNR) and are not detectable after a single stimulus presentation due to the presence of other neural activity and noise. While the normal EEG signal has a range of roughly 100 μV, ERP amplitudes are less than 10 μV and can thus not be detected easily. This is solved by two steps in the study design and subsequent analysis. The first step is the repitition of the same (or very similar) simulus throughout the experiment. This way, the ERP component is present multiple times in the EEG signal, making it easier to extract. The amount of repititions that is needed depends on the ERP component (i.e., specific subsections of the complete ERP waveform) of interest as their respective amplitude differs, as well as the amplitude of the non-ERP neural activity and remaining noise in the signal. For large ERP components such as the P300, 10 to 50 trials are needed to obtain reliable ERP components, while smaller components such as the P1 require more than 100 trials for their consistent extraction (Luck, 2014). The second step is the averaging of the trials. This process assumes that the evoked ERP is non-random (i.e., the

same ERP is generated by the same stimulus each time), while the remaining signal is random. When multiple trials are subsequently averaged, the random noise in the signal will be averaged out while the non-random ERP signal will remain, resulting in the final representation of the ERP waveform called the *grand averaged ERP*. A simple representation of the ERP extraction process is shown in Figure 16.

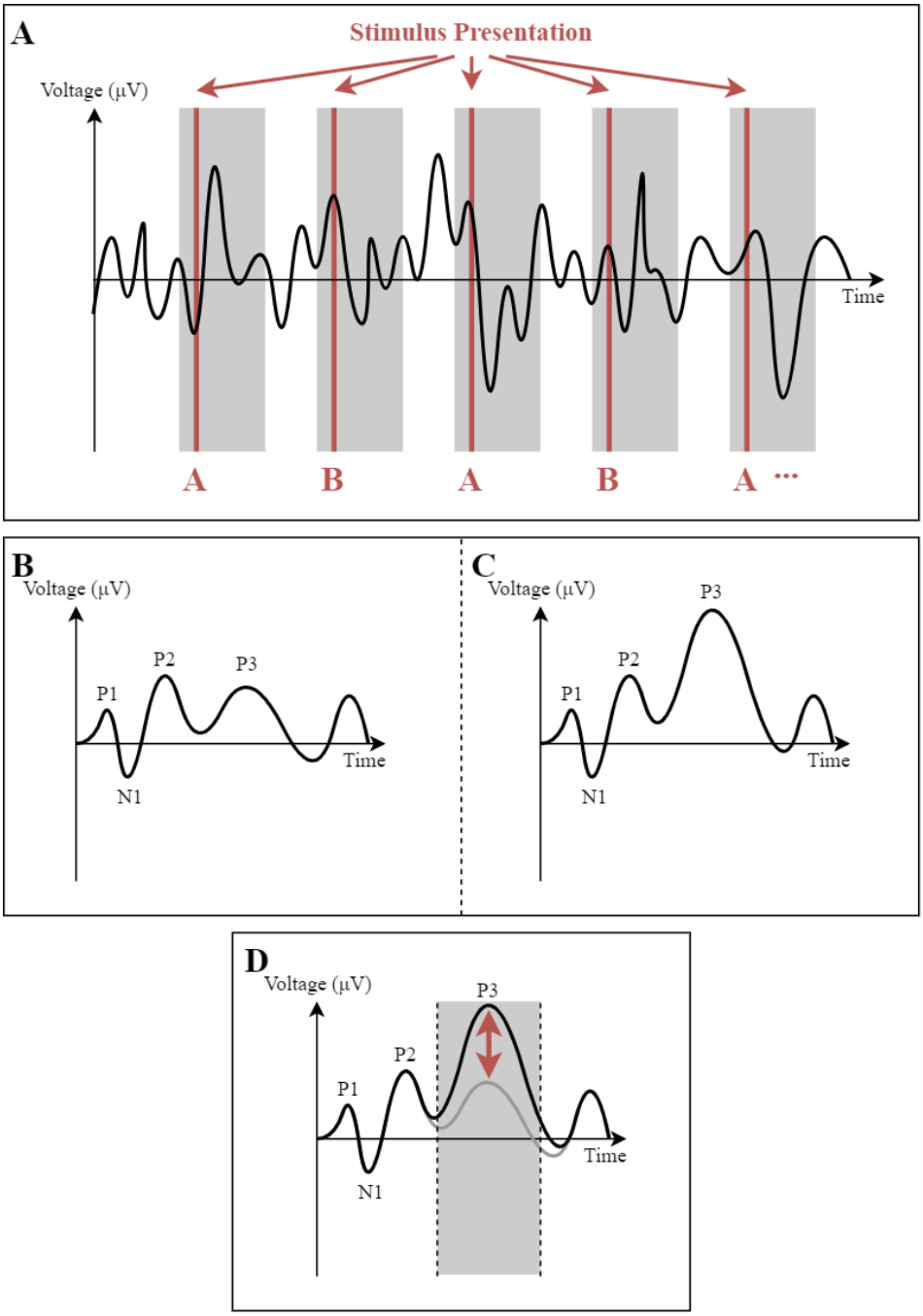

Figure 16: A visual representation of the steps needed to obtain an ERP waveform. **A)** An example of the EEG signal where stimuli are presented at certain intervals. The gray boxes show the extracted time windows for each trials. **B)** A hypothetical averaged ERP waveform for condition A. **C)** A hypothetical averaged ERP waveform for condition B. **D)** The grand averaged waveform of both conditions superimposed. The gray box indicated the time window containing the ERP component of interest (in this case, the P3). In this hypothetical case, the P3 in condition B is larger than in condition A.

As shown in Figure 16, the time window around each trial also includes a small amount of signal preceding the stimulus itself. This is done to *baseline correct* each trial. In brief, baseline correction is done as the overall signal amplitude throughout the trial might vary across trials due to non-ERP neural activity. The short time before the trial is averaged, and the average is subsequently subtracted from each time point (Luck, 2014). Considering the grand averaged ERP in Figure 16C, an ERP component can be defined by its *amplitude* (i.e., the size of the peak compared to 0, see Figure 17) and its *latency* (i.e., the time between the stimulus presentation and the peak of the component, see Figure 17). It is these aspects of the components that are most commonly investigated in ERP research. ERP research is a complex branch of neuroscience, and its analysis and interpretation is much more intricate as described above, but a more thorough explanation falls outside the scope of this dissertation. The interested reader is reffered to the following book: Luck, 2014.

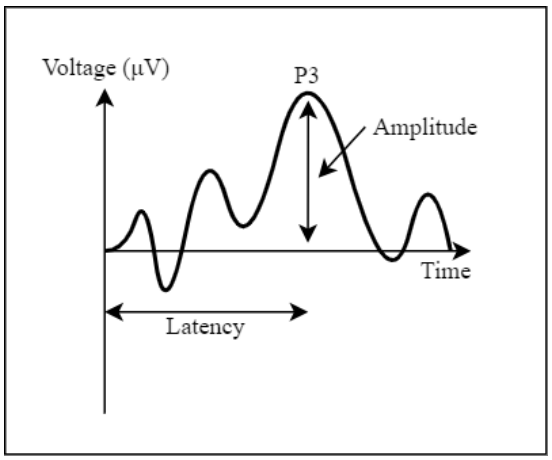

Figure 17: A visualization of the amplitude and latency of an ERP component.

2.2.4.6.2. Spectral power

As stated in section 2.1.4.4., the EEG signal is often divided into frequency bands. One of the most commonly conducted analysis methods is the investigation of how the power of the signals in specific frequency bands changes across time, conditions, or between specific groups of individuals. This analysis is called *spectral power*, and many variations exist in their computation. In chapter 4 and 5 of this dissertation, spectral power is computed using Welch's power spectral density (PSD) estimate, visualized in Figure 18 (Welch, 1967). Welch's spectral density estimate first divides the signal into time windows of equal length with overlap (see Figure 18A, where 50% overlap is employed). To avoid artifacts, each time window is subsequently multiplied with a hamming window (visualized in Figure 18B). For each time-windowed signal, the spectral density is computed using the fast fourier transform (see section

2.1.4.3.1.) of which the modulus is taken. The modulus is subsequently squared and computed for each frequency bin, see formula 8 where *S(f)* is the spectral density as a function of frequency *f*, *X(f)* is the fourier transform of a signal, || denotes the modulus, and *Δf* denotes the width of the frequency bins. The unit of the spectral density is $V^2.Hz^{-1}$. To obtain an average value of EEG power in a frequency band, the average is taken of the PSDs of each EEG segment.

$$S(f) = \frac{|X(f)|^2}{\Delta f} \quad (8)$$

As can be seen, PSD is a function of frequency bin width (i.e., the amount of energy per frequency unit that is present in the signal), and bin width is dependent on the sampling rate of the EEG. Bin widths are often less than 1 Hertz, so PSD can provide estimates for narrow frequency ranges, but is not commonly employed. Significant variability exists between and within individuals regarding the main oscillation of each frequency band (Dustman et al., 1999). Therefore, rather than extracting the power of one bin, multiple bins are averaged to obtain an average power of a frequency band (e.g., alpha power is the average power in the alpha frequency band).

Most EEG spectral power measures rely on this approach, but several adaptations can be made. In its current form (as described as above, see Figure 19B), the measure is known as *absolute power* (Cohen, 2014). While this measure is perfectly usable, it might introduce biases in the results as differences with regard to signal strength due to recording quality or skull thickness will lead to different values of absolute power that are not directly related to the underlying neural activity. Therefore a common adaptation is *relative power*, which simply divides the average power of a frequency band of interest by a predefined range of frequencies (see Figure 19C). Of note here is that the range should lie within the outer ranges of the bandpass filter apllied during preprocessing (section 2.1.4.3.1.). Additionally, absolute power measures of different frequency bands can be divided, resulting in a *power ratio* (see Figure 19D). While absolute power has a unit ($V^2.Hz^{-1}$), both relative power and power ratios are unitless. Relative power can be interpreted as *"How much energy of the EEG signal is concentrated in the currently considered frequency band"*, while a power ratio can be interpreted as *"What is the ratio of energy between two frequency bands of interest"*.

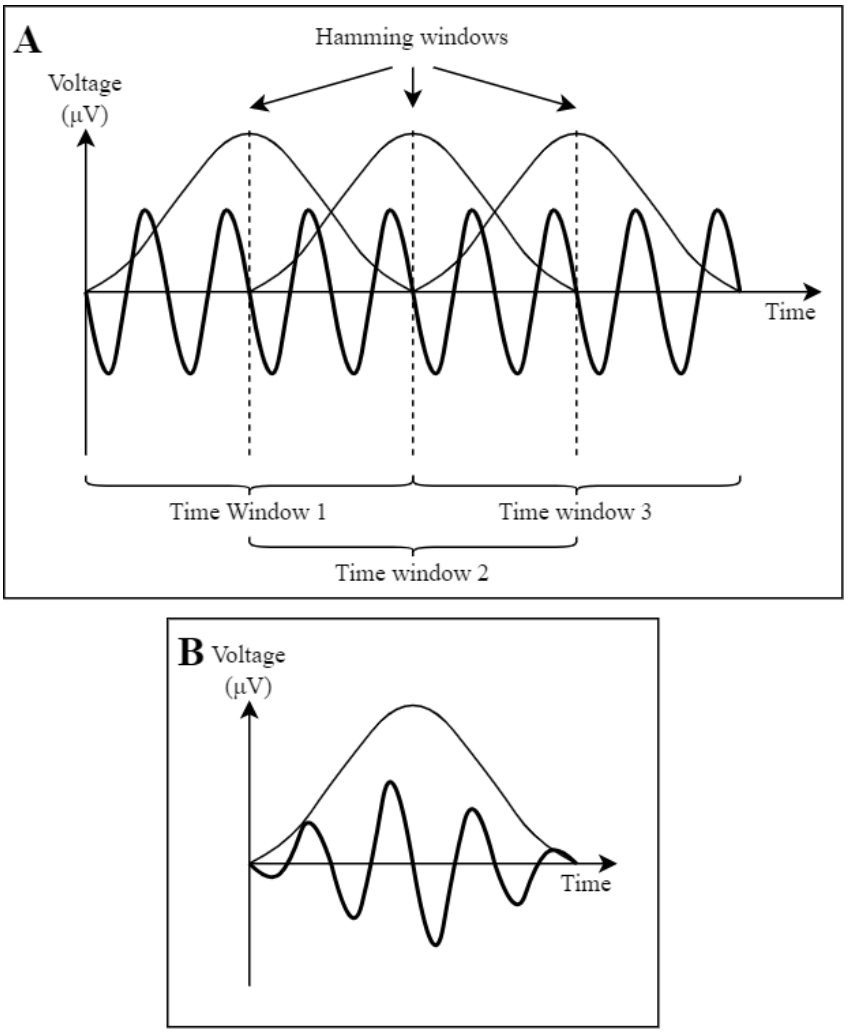

Figure 18: Visualization of the spectral power approach for EEG analysis. **A)** An EEG signal is divided into time windows of equal length, with 50% overlap to not lose information due to the applied hamming window. **B)** Resulting waveform due to the application of a hamming window. This results in a signal with zero amplitude at the edge of the waveform, thus minimizing ringing artifacts.

Power measures are perhaps the most commonly employed spectral EEG analysis method. This is likely due to two reasons. Firstly, power measures are easily calculated from both sensor and source time series. Secondly, power measures provide a relatively direct approximation of neural activity. As discussed in section 2.1.4.2., EEG measures synchronous postsynaptic potentials of large pyramidal neuron assemblies. Larger amplitudes of for example the alpha band can thus be interpreted as activity of postsynaptic potentials of either larger neuron assemblies, or more intense activity of neuron populations. One important note should be made here: in sensor space, power of electrodes is often assumed to reflect activity of the underlying cortical regions (e.g., frontal alpha activity is often assumed to reflect inhibition of frontal regions; Smith et al., 2017). These assumptions have been challenged as they likely underestimate the signal spread due to volume conduction, and it has been shown that alpha power at frontal electrodes is significantly influenced by occipital activity (Schaworonkow &

Nikulin, 2021). Interpreting power measures of electrodes as proxies of neural activity of near corticol regions should thus be done with severe caution.

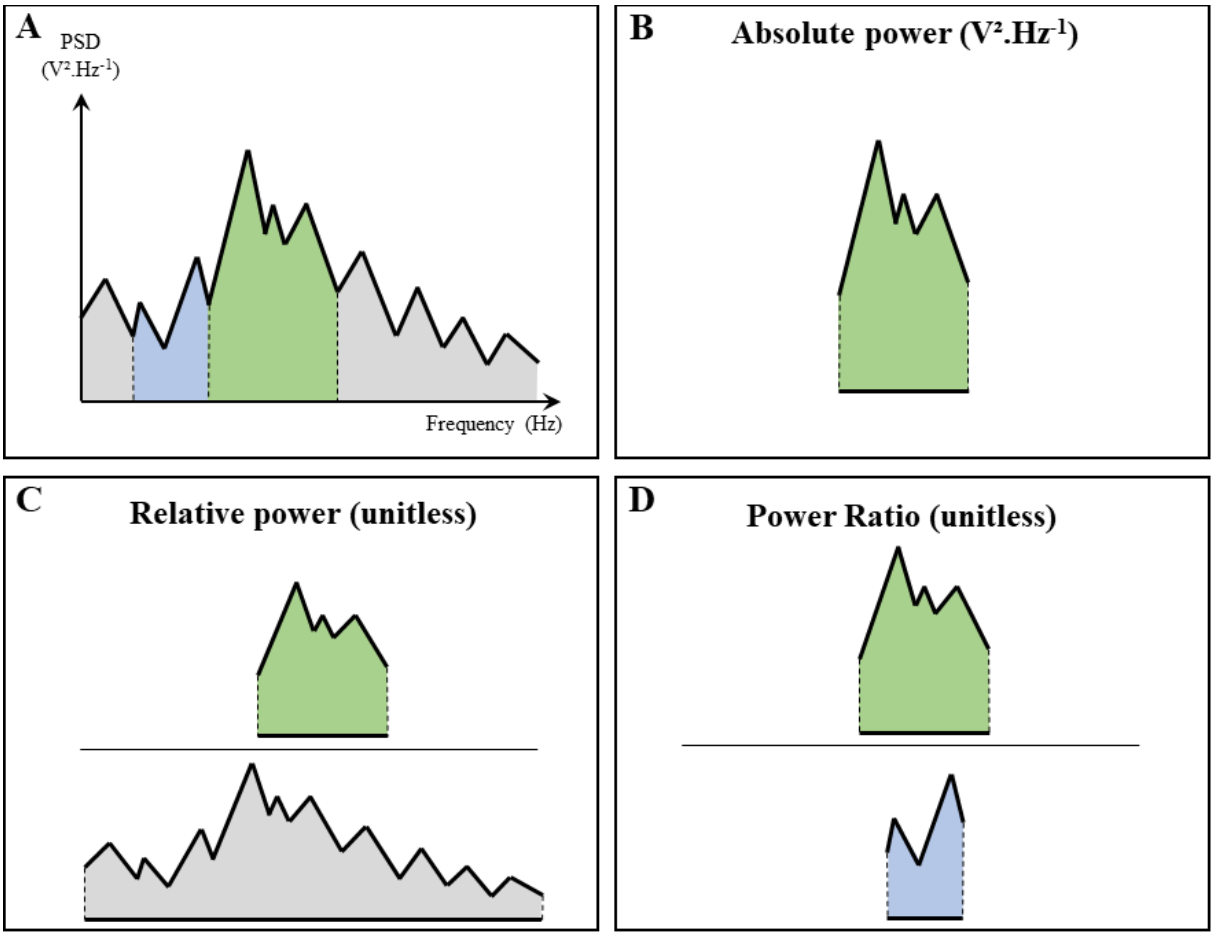

Figure 19: Conceptualization of the different power measures. **A)** A hypothetical Power Spectral Density estimate of an EEG signal. The alpha frequency band is shown in green, the theta band in blue. **B)** Absolute power. **C)** Relative power. **D)** Alpha-Theta power ratio.

2.2.4.6.3. Functional connectivity

The final discussed analysis method is functional connectivity (FC). To understand the basic premises of FC, one needs to consider how the brain is organized and functions. Two key principles are of interest here: *functional segregation* and *functional integration* (Friston, 1994). Functional segregation refers to the activity of specific regions of the brain during certain states (e.g., resting-tate, task-induced, sleep), and is interpreted as the specialization of brain regions for certain functionalities. This conceptualization of brain function has a strong historical background as lesion studies were among the first tools to investigate neural activity (Friston, 1994). Functional integration is the conceptualization of the brain as many brain networks that are interconnected on many scales, often called *connectionism* (Friston, 1994). Functional connectivity can be seen as the analysis method for assessing functional integration and thus assessing the connections and exchanged information between brain regions, formally defined by Friston as *"the assessment of statistical dependencies among remote neurophysiological events"* (Friston, 1994). Considering EEG, FC analysis refers thus to the detection of statistical dependencies across time between either different electrodes (sensor space FC) or different ROIs (source space FC). Given that data from both sensor and source space consists of time series, FC analyses can be applied in both spaces.

A multitude of FC measures have been developed that can be distinguished by their possible *directionality* and *linearity*, the amount of considered brain regions, and whether they assess functionality in the time or frequency domain. Directionality characterizes whether the measure infers the direction of information flow (i.e., *directed* FC measures) or not (i.e., *undirected* FC measures). Linearity characterizes whether the FC measures assess linear or nonlinear relationships. FC measures can further either consider the connection between two ROIs (i.e., *bivariate* measures) or multiple ROIs (i.e., *multivariate* measures). Finally, measures can assess the dependencies in the time- or frequency domain. A full description of the commonly employed FC measures is beyond of the scope of this dissertation, and only the employed FC measure *amplitude envelope correlation* (AEC) will be discussed, but the reader is referred to the following articles as a starting point: Bastos & Schoffelen, 2016; Chiarion et al., 2023; Sakkalis, 2011.

Amplitude envelope correlation is an undirected, linear, bivariate, time domain FC measure (Hipp et al., 2012). AEC assesses how the amplitude envelopes of two time series correlate across time and relies on the assumption that consistent increases and decreases in activity (reflected in amplitude changes across time) of ROIs in the brain indicates that these regions are communicating. AEC results in a single correlation coefficient, and thus has a range of [-1, 1]. Large AEC values (regardless of the sign) is an indication of strong functional connection between the two regions while AEC values near zero indicate little to no consistent information flow between the two ROIs. AEC can be considered a "simple" measure compared to other FC measures (e.g., Granger causality; Marinazzo et al., 2011, partial directed coherence; Baccalá & Sameshima, 2001, or directed transfer function; Kamiński et al., 2001), and the obtained information is limited compared to the aforementioned FC measures as AEC does not provide directionality nor does it consider more than two ROIs. The simplicity of the measure, however, is also an advantage as it requires little assumptions regarding the underlying information flow or involved cortical regions. This is especially advantageous when no a priori hypotheses are present regarding the involved regions or directionality of the neural communication, which was the case in chapter 4 and 5. Additionally, AEC has been identified as a reliable measure for resting-state network estimation, and outperformed more complex FC measures (Colclough et al., 2016). It should be noted, however, that this result was obtained from MEG, not EEG data, thus some caution should be taken.

The computation of the final AEC values from the time series starts with bandpass filtering both signals. This step isolates the oscillations in the frequency range of interest from other neural activity in the EEG signal. Subsequently, the bandpass filtered signals are pairwise orthogonalized using the Gram-Schmidt orthogonalization procedure (Leon et al., 2013). This step is conducted because the volume conduction of the EEG signal results in the zero-lag presence of (partly) the same neural activity in either multiple electrodes (sensor space) or close ROIs (source space, due to the spreading from the smoothness constraint). If this common signal is not extracted, AEC would result in falsely inflated FC measures that bias the results as AEC values would partly become a function of distance between ROIs. Gram-Schmidt orthogonalization orthogonalizes the time series by considering them as *N-dimensional* vectors (with N being the amount of timepoints). Time series 2 (V_2) is projected on time series 1 (V_1)

using formula 9, where $proj_{V1}(V_2)$ denotes the projection of V_2 on V_1 and $\langle\ \rangle$ denotes the dot product.

$$proj_{V_1}(V_2) = \frac{\langle v_2, v_1 \rangle}{\langle v_1, v_1 \rangle} V_1 \quad (9)$$

This projection is subsequently subtracted from V_2, resulting in the orthgonalized timeseries 2, $V_{2\perp V1}$ (see Figure 20 for a visual explanation). Of note here is that this orthogonalization leaves time series 1 unaltered, and is thus order dependent. To obtain a bias free estimate, this orthogonalization is thus conducted twice with switched time series, and all subsequent steps are performed for each pair of orthogonalized time series. The final AEC value for each pair is averaged to obtain the final AEC value representing the connection strength. Of note here is that simulations have shown that spurious connections might still be present even after removal of the zero-lag common signal (Palva et al., 2018). After orthogonalization, each time series is transformed using the Hilbert transform. The absolute value of the Hilbert-transformed signal is subsequently taken, which results in the envelope of the signal (Hipp et al., 2012). The correlation coefficient is subsequently computed from the envelopes, resulting in the AEC value. A visual representation of the different steps is shown in Figure 21.

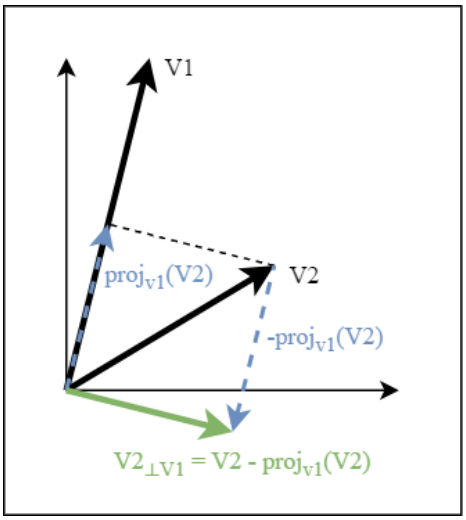

Figure 20: 2D representation of the Gram-Schmidt orthogonalization process.

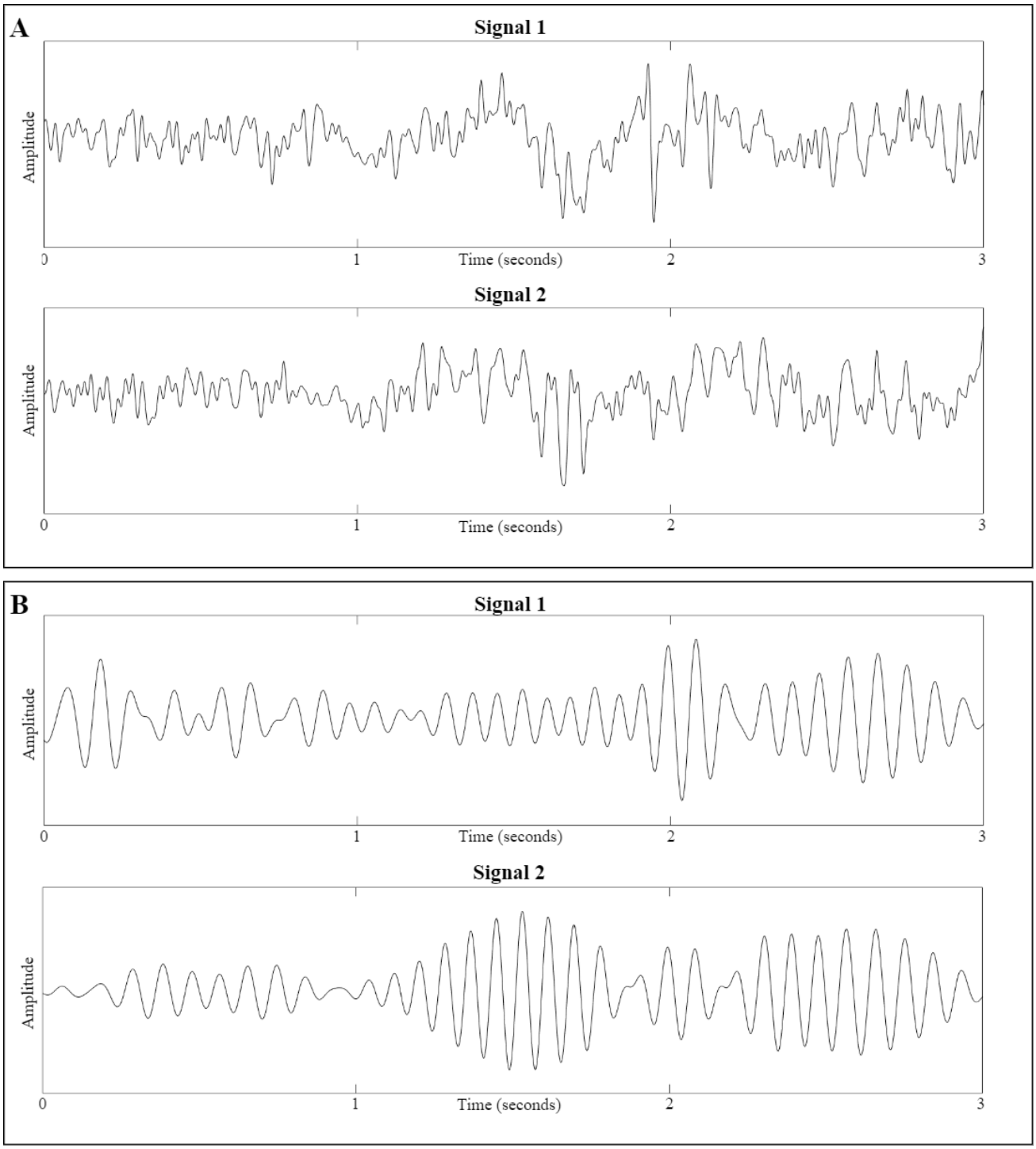

Figure 21: Visualization of the steps to obtain amptlitude envelope correlations from two EEG signals. **A)** Two EEG signals. **B)** The bandpass filtered EEG signals in the alpha frequency range (8-13 Hz).

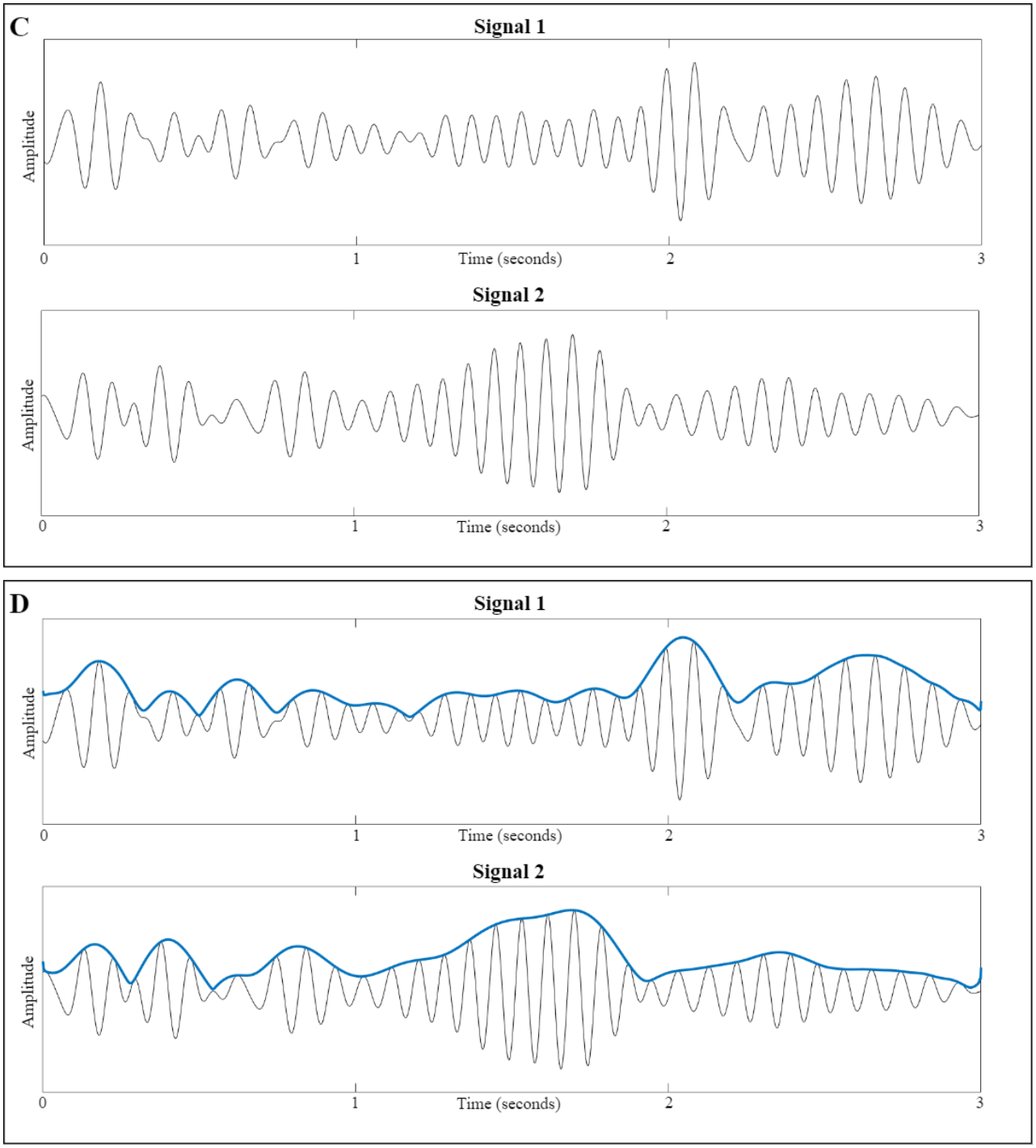

Figure 21 (continued): Visualization of the steps to obtain amptlitude envelope correlations from two EEG signals. **C)** Orthogonalized time series (of note: signal 1 did not change, but signal 2 did, showing the order dependence of the orthogonalization procedure). **D)** The amplitude envelopes from the orthogonalized signals superimposed in blue. The correlation coefficients from both amplitude envelopes results in the final AEC value.

2.2.4.7. Advantages and disadvantages of EEG

EEG has several advantages compared to other neuroimaging techniques. First and foremost is its high temporal resolution which makes it possible to investigate neural activity in timeframes that are not accessible by other modalities such as fMRI, PET or SPECT. This high temporal resolution is accompagnied by the possibility of measuring whole-brain activity when a large number of electrodes are used, thus providing researchers with a time-sensitive and temporally rich representation of neural activity. Additional advantages are that EEG is completely non-invasive (contrary to PET or SPECT) and is low cost (contrary to fMRI). Comparing EEG to fMRI specifically, additional advantages can be identified. EEG measures neural activity directly, contrary to the assessment of the BOLD response with fMRI. EEG further allows the participants to be seated (and recently, even to move around; Lau-Zhu et al., 2019), while participants need to lie down in the MRI scanner. This freedom regarding participant position and movement makes it possible for EEG to be employed in more naturalistic paradigms with real-life interactions, contrary to the strict limitations of fMRI. The small bore of the MRI scanner in which the participant is located presents another complication not present with EEG, it might make individuals claustrophobic. This is especially difficult for children, as the loud noises and small bore might frighten them. Additionally, EEG is completely silent making research into the auditory system much easier compared to fMRI.

There are however some disadvantages that should be acknowledged. Most important is the lower spatial resolution of EEG compared to fMRI. Although ESI provides an acceptable resolution for many research interests, the fact that spatial resolution decreases as a function of distance to the scalp makes it difficult to investigate deeper brain structures (e.g., amygdala, hippocampus) and inherently limits EEG research to more superficial cortical structures. Comparing EEG and fMRI again, three additional disadvantages should be noted. First is the fact that preparing participants generally takes longer as the electrodes and possibly gel needs to be applied and tested for acceptable impedance. Second is the fact that hair types have a significant influence on the quality and even possibility of collecting EEG data (Etienne et al., 2020; Lees et al., 2023). Third is that signal quality can degrade throughout a recording, an issue especially present when sponge electrodes are employed as the water in the sponges dries quickly, therefore limiting the possible duration of a paradigm. .

3. Objectives of the dissertation

The main objectives of this dissertation are twofold. Firstly, the current state of the research field regarding acute psychosocial stress and EEG is cricitally reviewed. Secondly, the possible added value of ESI is assessed by evaluating the influence of psychosocial stressors *in isolation* on both sensor- and source level EEG measures, and investigating the effect of different psychosocial stressor paradigms on source level EEG measures reflective of commonly implicated ROIs in the neural psychosocial stress response. The spatially precise results obtained from the vast fMRI literature regarding the neural psychosocial stress response are thus extended with the temporally richer representation of neural activity inherent of EEG through the usage of ESI. Although the presence of EEG as a neuroimaging technique is increasing in the research field of psychosocial stress (Giannakakis et al., 2019; Katmah et al., 2021; Vanhollebeke et al., 2022), ESI is not commonly employed yet, making the studies discussed in chapter 4 and 5 of this dissertation among the first ones that conduct ESI research focused on the acute psychosocial stress response.

The first objective is encapsulated by chapter 2 and 3. The main objective of **chapter 2** is assessing and reviewing the current state of the spectral analysis EEG-psychosocial stress research field. Chapter 2 thus describes the results of a systematic review of the studies that employed spectral analyses as well as their results (Vanhollebeke et al., 2022). This chapter further provides the framework for the experimental studies presented in chapter 4 and 5 by identifying the most commonly investigated frequency bands and employed analysis techniques, and evaluates their robustness through meta-analyses. In **chapter 3**, a specific subfield of EEG-psychosocial stress research is reviewed, the ERP-Cyberball literature (Vanhollebeke, Aers, et al., 2023). The main objective of this chapter is assessing whether the results of studies evaluating ERP components during the Cyberball are reflective of an ostracism-specific neural alarm system, or if other neural mechanisms not specific to ostracizing stimuli, possibly evoked by other characteristics of the paradigm aside from the overarching social context of ostracism, are the driving force of these results. This objective is is not only important within the field of ERP research, but has also been a point of discussion in the fMRI field for a significant amount of time (Mwilambwe-Tshilobo & Spreng, 2021; Somerville et al., 2006; H. Wang et al., 2017).

The second objective is investigated in chapter 4 and 5. The main objective in **chapter 4** is evaluating whether a purely psychosocial stressor, without the influence of co-occuring, non-psychosocial stressors such as time pressure or cognitive demanding tasks that are often present in psychosocial stress paradigms, is capable of eliciting significant differences in both sensor level and source level EEG measures. This is of high importance as the commonly employed sensor level EEG measures frontal theta, alpha, and beta power often change similarly due to these co-occuring stressors alone, without the presence of a psychosocial stressor (Ehrhardt et al., 2021). ESI is further employed to investigate whether power changes in ROIs commonly found in fMRI studies are more sensitive to psychosocial stressors than the aforementioned sensor level measures, and AEC is employed to investigate whether ROI functional connectivity is affected by psychosocial stressors alone. To assess this as best as possible, a within-subjects design is employed using a large participant sample. The objective of **chapter 5** is evaluating the similarities and dissimilarities between neural psychosocial stress responses evoked by different paradigms. This is again investigated with a within-subjects design where a large participant sample is exposed to the Cyberball and MIST on different days. Similar to chapter 4, power changes in severel ROIs identified by the fMRI literature are investigated with ESI after stress exposure and compared to an active control condition, and AEC is employed accordingly for further insights in the possibly differential stress responses.

Together, the studies presented in this dissertation moves the field forward by **1)** reviewing the current literature and addressing possible underlying limitations that hinder further progression in our understanding of the neural psychosocial stress respons, and **2)** providing evidence that ESI is an important analysis technique that aids the psychosocial stress research field by combining the high spatial resolution from fMRI with the high temporal resolution of EEG.

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Chapter 2

The neural correlates of psychosocial stress: a systematic review and meta-analysis of spectral analysis EEG studies

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Abstract

Whereas the link between psychosocial stress and health complications has long been established, the influence of psychosocial stress on brain activity is not yet completely understood. Electroencephalography (EEG) has been regularly employed to investigate the neural aspects of the psychosocial stress response, but these results have not yet been unified. Therefore, in this article, we systematically review the current EEG literature in which spectral analyses were employed to investigate the neural psychosocial stress response and interpret the results with regard to the three stress phases (anticipatory, reactive, and recovery) in which the response can be divided. Our results show that three EEG measures, alpha power, beta power and frontal alpha asymmetry (FAA), are commonly utilized and that alpha power consistently decreases, beta power shows a tendency to increase, and FAA varies inconsistently. We furthermore found that whereas changes in alpha power are independent of the stress phase, and changes in beta power show a relative stress phase independent trend, other EEG measures such as delta power, theta power, relative gamma and theta-alpha power ratio show less stress phase independent changes. Meta-analyses conducted on alpha power, beta power and FAA further revealed a significant effect size (hedge's $g = 0.6$; $p = 0.001$) for alpha power, but an insignificant effect size for beta power (hedge's $g = -0.31$; $p = 0.29$) and FAA (hedge's $g = 0.01$, $p = 0.93$). From our results, it can be concluded that psychosocial stress results in significant changes in some spectral EEG indices, but that more research is needed to further uncover the precise (temporal) mechanisms underlying these neural responses.

1. Introduction

Throughout recent years, the incidence of mental health problems has risen worldwide (Liu et al., 2020). The recent outbreak of COVID-19 further exacerbated the major challenges regarding mental health due to its large impact on both society (economic uncertainty) and on a personal level (loss of close friends/family and social isolation) (Salari et al., 2020). An important factor in the current problems regarding mental health is stress, the latter being an important catalyzer of mental disorders such as depression and anxiety disorders (Daviu et al., 2019; Mazure, 1998). Stress can be defined as the perception of personal or environmental stimuli as more taxing than the direct mitigating capability of the body, which results in an acute stress response in the body (Folkman and Lazarus, 1984). A key player in the stress response is nevertheless the brain, which alters various effector systems mainly through the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adreno-medullar (SAM) axes, resulting in physiological (such as increased heart rate and blood pressure) as well as psychological changes (Dickerson and Kemeny, 2004; Godoy et al., 2018; Kudielka and Kirschbaum, 2005; McEwen and Seeman, 1999).

One specific stressor subtype, the psychosocial stressor, seems to have a prominent role in the stress-disease link, making it an important subject for extensive research (Back´e et al., 2012; Greenwood et al., 1996; Kemeny and Schedlowski, 2007; MD et al., 2002; Siegrist, 2008). In the current paper, based on a review of the literature, we define psychosocial stressors as *"threatening or stressful stimuli arising from social interactions mainly due to their novel, unpredictable or uncontrollable characteristics or the presence of social-evaluative threats"*. Psychosocial stress can then be defined as the result of a cognitive appraisal or interpretation of a psychosocial stressor that taxes or exceeds the coping capabilities of an individual. The crucial role of psychosocial stressors as contributors to stress-imposed (mental) health complications has multiple reasons (Epel et al., 2018; Kogler et al., 2015). From an evolutionary point of view, humans are a social species, making social interactions and the need to belong innate properties of every individual (Baumeister and Leary, 1995). Psychosocial stressors may disrupt these core human needs and are therefore highly impactful on the general well-being of a person. Furthermore, psychosocial stressors are not limited to a specific part of an individual's life, as everyday life consists of an abundance of social interactions. This makes chronic exposure to psychosocial stressors more probable compared to other types of stressors such as physical stressors (e.g. receiving electrical shocks) or cognitive stressors (e.g. reaction time

tasks), further explaining its dominant presence in stress-related diseases (Dupre et al., 2015; Melchior et al., 2007; Phelan et al., 1991; Tennant, 2001).

It is noticeable that various articles investigating the response to psychosocial stressors do not investigate the stress response in its entirety, but rather focus on specific phases of it. This subdivision of the acute stress response in discrete phases is logical as various distinct neurological, psychological, and physiological processes are active throughout the stress response. When identifying different phases of an acute stress response as a function of its occurrence in time in relationship to the present stressor, three phases become apparent: the *anticipatory*, the *reactive*, and the *recovery* phase (see Figure 1). The existence of distinct phases in the acute stress response has long been established, and the allostatic load theory has defined how repeated exposure to stressors can lead to maladaptive trajectories of these phases such as the lack of adaptation (abnormal reactive phase) or a prolonged response to stressors (abnormal recovery phase) (Juster et al., 2010; McEwen and Seeman, 1999). The first phase, the *anticipatory* phase, can be defined as the moment a person is aware of the upcoming stressor, but is not yet directly exposed to it. This phase is defined by a high uncertainty about the near future and the possible presence of a social evaluative threat, therefore evoking a stress response (Engert et al., 2013). The second phase, the *reactive* phase, is defined as the time when an individual is directly exposed to the stressor. It could be argued that the anticipatory and reactive phase of the stress response can be seen as one, since uncertainty and social evaluative threat are present in both phases, but this distinction is valid since in the reactive phase, participants are actively engaged with the actual stressor whereas during the anticipatory phase they might not be. The third phase that can be defined is the *recovery* phase and starts directly after the ending of the stressor exposure. The difference between this phase and the anticipatory and reactive phase is larger, since the uncertain, uncontrollable, and socially evaluative threatening stimuli are no longer present. The recovery phase therefore consists mainly of the possible reversal of psychological and physiological alterations caused by the stressor. Depending on the physiological measure, the duration of these restorations can take from 30 min to 1 h (i.e., cortisol, Goodman et al., 2017) to up to 2h (i.e., functional magnetic resonance imaging, Vaisvaser et al., 2013; van Oort et al., 2017). Although all three phases may contain unique alterations in physiological and psychological mechanisms, these alterations are all induced by the same underlying mechanism, namely, the evoked stress response due to the presence of a psychosocial stressor.

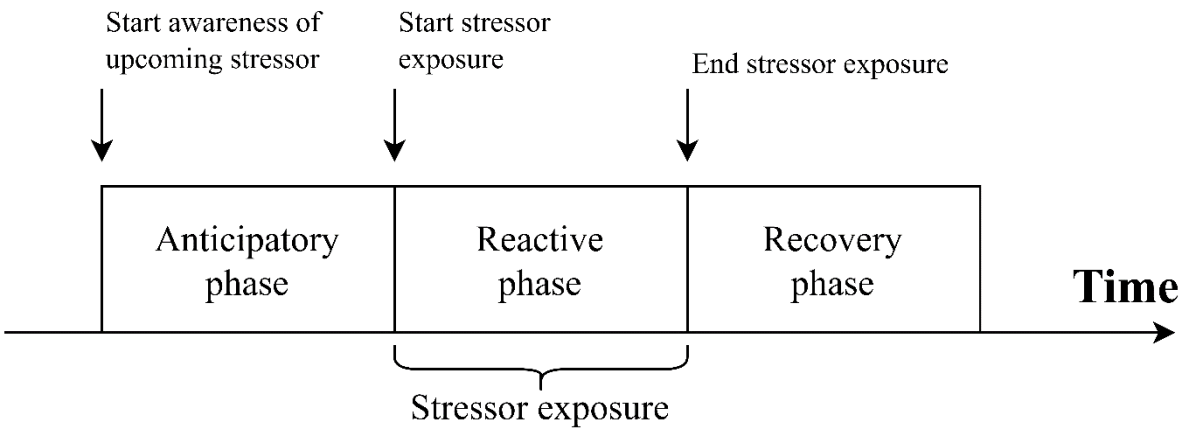

Figure 3: The three stress phases of the stress response with regard to time.

The pivotal role of the brain as the orchestrating organ of the different phases of the psychosocial stress response, makes the brain a principal focus of (psychosocial) stress-related studies (McEwen, 2007; McEwen and Gianaros, 2011). A central investigative tool in this research endeavor has been the use of neuroimaging, with the most commonly used neuroimaging methods in stress research being *functional magnetic resonance imaging* (fMRI) and *electroencephalography* (EEG). fMRI has, due to its high spatial resolution, mostly been employed to identify the involved brain regions in the psychosocial stress response. The main findings from these efforts are the involvement of three major brain networks (the default mode, salience and central executive network; for reviews see Kogler et al., 2015; van Oort et al., 2017) as well as a bilateral cluster comprising the insula, claustrum, and inferior frontal gyrus (for a review, see Berretz et al., 2021). EEG has, due to its high temporal resolution, been employed to investigate the more time-sensitive aspects of the neural response to psychosocial stress. EEG studies investigating the neural psychosocial stress response either focus on event-related potentials (ERPs) or analyze changes in the prominent oscillations present in the EEG signal through spectral analysis methods. ERP analyses focus on short-term (mostly within 1 s), *task-evoked variations* in neural activity in response to sensory stimuli and investigate known event-related potential components such as the N2 and P3 (Cohen, 2014; Kawamoto et al., 2013; van der Veen et al., 2016). The main drawback of ERP analysis, if applied to the investigation of the various phases of the psychosocial stress response, is its dependency on clearly defined stimuli, thus limiting its application potential for uncovering the whole neural response to stressful stimuli. This limitation is not shared by spectral analysis methods, since these methods can be applied to either the stimulus-defined time windows to investigate task-evoked neural activity, but also longer, continuous EEG recordings for the investigation of *task-*

induced variations in neural activity. Therefore, spectral analyses that investigate EEG signal properties in both the time and frequency domain (Cohen, 2014) are more useful to fully investigate the different phases of stress response. Various spectral analyses have been applied to investigate psychosocial stress-related variations in the delta (0.5–4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (15–30 Hz) and gamma (>30 Hz) frequency bands (although the exact ranges can vary across articles). The most common spectral analysis technique is spectral band power, which calculates the average power in a specific frequency band and is reflective of the neuronal activity in this frequency range (Cohen, 2014). Commonly studied frequency bands are the theta band, linked to working memory functionality, sensory and motor processing, cognitive interference, and emotional memory consolidation during sleep (Karakaş, 2020; Klimesch, 1999; Nigbur et al., 2011; Nishida et al., 2009); the alpha band, believed to be inversely correlated with cortical activity and reflecting coordination mechanisms of brain networks (Allen et al., 2004; Jensen and Mazaheri, 2010; Mathewson et al., 2011) and the beta band, associated with attention and sustaining the current cognitive or sensorimotor state (Engel and Fries, 2010; Wróbel, 2000). Another spectral analysis technique commonly selected is frontal alpha asymmetry (FAA), generally obtained by subtracting the natural log transformed alpha power value of a left frontal electrode (mostly F3 or F7) from that of a right frontal electrode (mostly F4 or F8), which is indicative of the relative difference in alpha power between the frontal parts of the left and right hemisphere. It is suggested that a relative higher left hemispherical activity indicates a tendency for approach-oriented behavior and that relative higher right hemispherical activity signifies more withdrawal-oriented behavior (Smith et al., 2017). FAA is ubiquitous in psychological and psychiatric EEG research and has been linked to a wide variety of psychological constructs and psychiatric disorders (Smith et al., 2017). Most commonly studied are the relationships between FAA and motivational/emotional variables or psychiatric disorders such as depression and posttraumatic stress disorder (Allen et al., 2004; Meyer et al., 2015; Smith et al., 2017; van der Vinne et al., 2017). Research suggests that FAA changes on a group level are variable and are highly dependent on a variety of factors such as personality traits, age and gender (Coan et al., 2006; Miller et al., 2002; Stewart et al., 2010; van der Vinne et al., 2017). Moreover, a recent review shows that stress influences hemispheric laterality in both animal and human brains, where stress seems to mostly induce higher activity in the right hemisphere (Ocklenburg et al., 2016). A proposed explanation of the varying results by Ocklenburg et al. (2016) might then be that acute stressors generally induce higher right hemispherical activity, and that depending on the hemispheric dominance of the cognitive functions performed by the brain during the presence of a stressor, FAA might

increase or decrease. An article by Berretz and colleagues (2020) further suggests that stress is highly influential in both the development of psychiatric disorders as well as the alteration of hemispheric laterality, further showing the relevance of FAA as an EEG index for psychosocial stress. Aside from FAA, other power-derived measures are utilized such as relative gamma and the theta/alpha ratio (Minguillon et al., 2016; Subhani et al., 2013). More complex spectral analysis methods, such as functional connectivity (FC), which investigates the temporal relationships between distinct neurophysiological events (Friston, 1994), are also explored, but to a lesser extent. Only three functional connectivity measures, phase-amplitude coupling, amplitude-amplitude correlation, and coherence have been reported (Poppelaars et al., 2018, 2021; Subhani et al., 2016a, 2016b).

Although the current body of literature using spectral EEG measures to identify the neural processes related to psychosocial stress is substantial, to our knowledge a systematic review and meta-analysis is currently lacking, making it difficult to have a concise overview of what has been undertaken and uncovered. Interestingly, two reviews have been recently published which review EEG results regarding the more general concepts of mental/psychological stress. Katmah and colleagues (2021) reviewed articles focusing on the detection of mental stress through means of machine learning algorithms. Although some overlap exists between this review and the current article regarding included articles, due the more technical focus on the machine learning algorithms used to detect mental stress, Katmah et al. (2021) employed a broader definition of mental stress, did not differentiate between the different phases of the stress response when interpreting the results and did not conduct meta-analyses. In another review, Giannakakis et al. (2019) examined the different physiological measurement possibilities for stress detection. However, similarly to Katmah et al. (2021), a more general definition of psychological stress is employed and no differentiation between stress phases nor meta-analyses are present. For the reader interested in mental stress detection through means of EEG or the possibilities regarding physiological stress measurement options, we refer to the aforementioned articles.

In this paper, we focus on the three (anticipation, reactive, and recovery) phases of the stress response induced by acute (short-term) laboratory (conducted in a controlled environment) psychosocial stressors in healthy, unmedicated adults measured using EEG and interpreted with spectral analysis methods. The main research questions investigated in this systematic review are: *1)* Which spectral EEG measures have been employed in the investigation of the psychosocial stress response; *2)* Whether the identified spectral EEG

measures are stress phase-sensitive or phase-independent. In the subsequent meta-analyses, performed for alpha power, beta power, and FAA, the main research question is if changes in these EEG measures induced by acute laboratory stressors result in a significant effect size, regardless of the stressor phase in which they have been investigated.

2. Materials and methods

The guidelines of *The Preferred Reporting Items for Systematic Reviews and Meta-Analyses* statement (PRISMA, Moher et al., 2009) were followed and a protocol was designed and registered in the PROSPERO database (registration number: CRD42020177226, registration date: April 7th, 2020). During the first screening of the obtained papers, a small adjustment to the protocol, the inclusion of the additional search term *"criticism"*, was made (PROSPERO registration date: July 9th, 2020). The PRISMA flow diagram is shown in Figure 2.

2.1. Search strategy

Three databases, The National Library of Medicine (MEDLINE-PubMed), Web of Science and Embase, were searched to find articles whose content matched with the defined research questions. The keywords used for this search strategy are closely aligned with those of Kogler et al. (2015), with the following basic structure: ("Electroencephalography" OR "Electroencephalogram" OR "EEG") AND ("Stress" OR "Social Exclusion" OR "Social Rejection" OR "Ostracism" OR "Social Pain" OR "Criticism"). The choice of using "Stress" and its derivatives as the main term rather than "psychological" or "psychosocial stress" was made due to the lack of consistent typology in the literature (Epel et al., 2018). The full search strategy can be found in the PROSPERO registration.

2.2. Study selection

All obtained articles were firstly reviewed based on the title/abstract and later based on the full text independently by two reviewers (G.V. and S.D.S.). Inclusion/exclusion disagreements were resolved by reaching a consensus between both reviewers. Only studies that reported data of unmedicated healthy adults (18 years and older with no history of neurological or psychiatric disorders) that were exposed to an acute laboratory psychosocial stressor (as defined in the introduction) and underwent an EEG recording within 24h after the stressor exposure were included. Papers that investigated event-related potentials were included only if a spectral analysis was performed on the stimulus-defined time windows. Other results regarding latencies or amplitudes of ERP components discussed in the included articles are not discussed in the current review article. Studies that employed an acute psychosocial stressor, but used other neuroimaging methods (eg. fMRI, fNIRS) combined with EEG were included when the results of the EEG data were reported separately. Studies that investigated specific populations

(eg. psychiatric patients, specific metabolic interactions (eg. pharmacological interventions) or specific interventions (eg. meditation), but also included a control group satisfying the previously defined criteria were also included if the data of the control group was reported separately. The authors of studies that did not report data of the EEG results or control groups separately were contacted and these studies were included when additional data was provided. Review articles, meta-analyses, conference proceedings, editorials, letters, case reports, or non-peer-reviewed articles were excluded. Conference abstracts were also excluded, but the authors were contacted and asked if a publication had been completed from the work of the abstract. No limitation on the publication date was imposed. All articles until April 8th, 2021, were included.

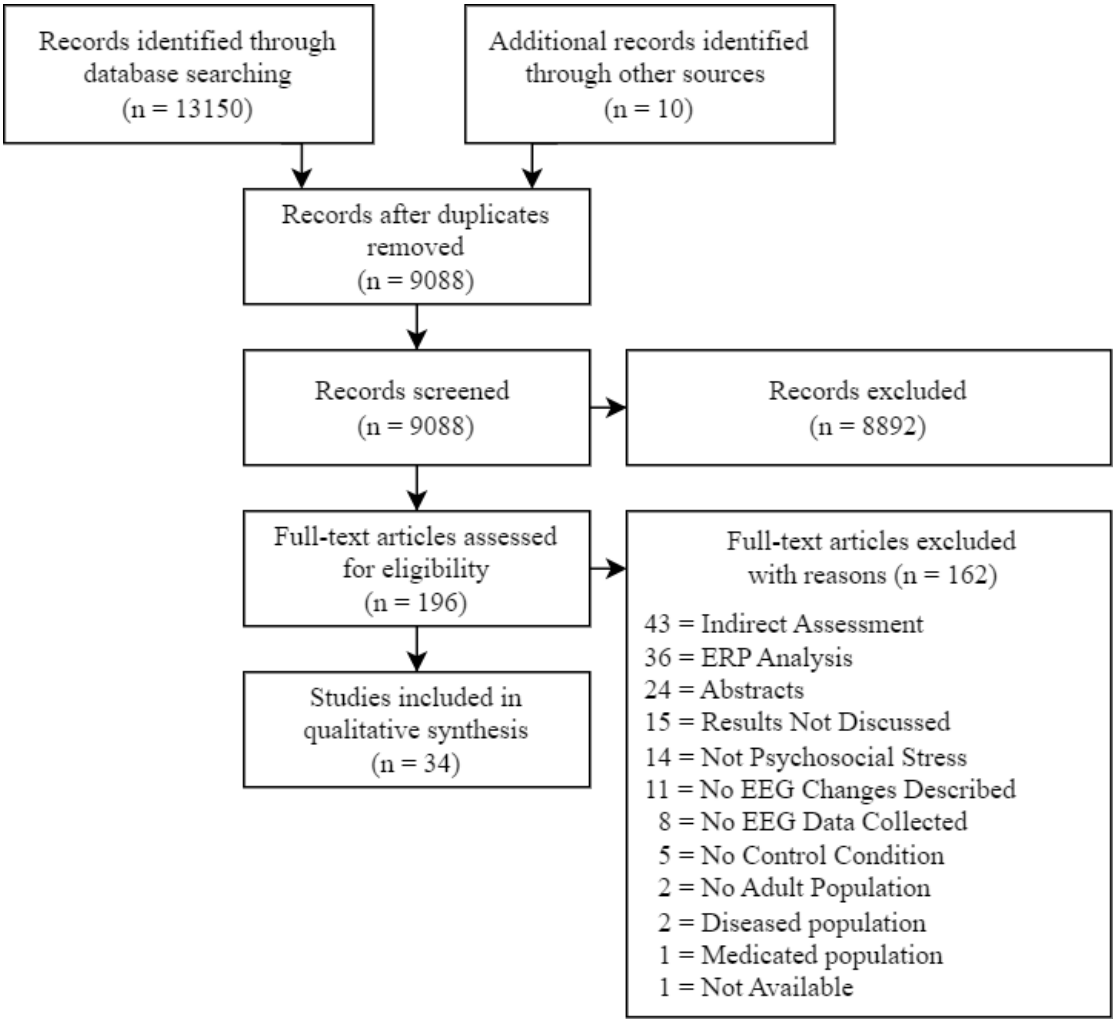

Figure 2: The preferred reporting items for systematic review and meta-analyses (PRISMA) flow diagram.

2.3. Quality assessment and risk of bias analysis

Quality assessment and risk of bias analysis of the included papers was done using an adapted version of the Standard Quality Assessment Criteria for evaluating primary research papers from a variety of fields (Kmet et al., 2004). This assessment tool consists of 14 questions that investigate the various aspects of an article regarding comprehensibility, reproducibility and validity. For each question, three answers are possible: yes (= 2) if the article reports all necessary information, partial (= 1) if some information is reported, but not all, and no (= 0) if the information is not present. A final score is obtained by summing all separate scores and dividing the final score by the maximum amount of points possible. A list of the used questions as well as the reasoning for the scoring of each question can be found in the supplementary materials (section 7.6.1.). The results of the risk of bias assessment are discussed in section 3.2.

2.4. Data extraction

Data from the included articles were extracted by one reviewer (G. V.) and were checked by a second reviewer (S.D.S.). The following variables were extracted: population demographics (sample size, mean age + standard deviation, men/women distribution, inclusion and exclusion criteria, recruiting method), experimental protocol (study type, stressor type, control condition, cover story, timing considerations), EEG recording specifics (amount of EEG channels, equipment brand, electrode placement position, impedance values, presence of Figure 2. The preferred reporting items for systematic review and meta-analyses (PRISMA) flow diagram. electrooculography (EOG) electrodes, sampling rate, online reference), EEG analysis specifics (downsample frequency, low pass frequency, high pass frequency, utility frequency removal procedure, interpolation procedure, offline reference, artifact removal procedures, epoch length, EEG analysis method), additional physiological data collection (cortisol, heart rate, heart rate variability (HRV), electrodermal skin activity (EDA), blood pressure, respiratory rate (RR), state questionnaires and whether or not these measures changed significantly), EEG-related results (test value (T-test or F-test), p-value, effect size and a short summary) and (if present) a priori sample size or power calculations. This information can be found in the supplementary materials (section 7.6.3.).

2.5. Data analysis

Three EEG measures, frontal alpha asymmetry (FAA), alpha power, and beta power, were selected for meta-analyses as these measures were utilized in more than five articles (FAA:

13 articles, alpha power: 12 articles, beta power: 8 articles; Tufanaru et al., 2015). Although theta power was also utilized in a sufficient number of articles (i.e., 6 articles), no meta-analysis was conducted for this EEG measure due to an important difference between the articles. Three articles calculated theta power from stimulus-locked epochs and investigated stimulus-evoked neural activity whereas the other three articles used continuous EEG data which was not stimulus-locked. Although it is likely that some relation exists between the mechanisms underlying evoked and induced neuronal activity, it remains difficult to accurately compare the obtained power values from each response type (David et al., 2006). When no relevant values (means + standard deviations) were given in the articles, the authors were contacted and if no response was obtained, values were extracted from the figures using GRABIT, a MATLAB toolbox designed for extracting data points from figures (Jiro, 2021). Both the data extraction method for each paper in the meta-analyses and the obtained values for the meta-analyses can be found in the supplementary materials (section 7.6.4.; section 7.6.5.). Data in several articles were pooled to obtain a single value for the EEG measure using formulas 1 and 2. In both formulas, n_i denotes the number of participants in study i.

$$Mean_{pooled} = \frac{\sum_{i=1}^{k}(n_i mean_i)}{\sum_{i=1}^{k} n_i} \quad (1)$$

$$Variance_{pooled} = \frac{\sum_{i=1}^{k}(n_i-1)variance_i}{\sum_{i=1}^{k}(n_i-1)} \quad (2)$$

Since different articles report results from different phases of the stress response (anticipatory, reactive, recovery), values for the meta-analyses are defined as the difference between the mean value from a phase of the study in which no psychosocial stressor is present (*baseline*: recording at the start of the experiment; *control condition*: a participant performs a task without the additional presence of a psychosocial stressor) and the mean value from a phase of the study where a psychosocial stressor is present (*anticipatory phase*: a participant is aware of the upcoming task; *reactive phase*: a participant is directly exposed to a psychosocial stressor) or where the effects of a psychosocial stressor are still present (*recovery phase*: right after a participant has been exposed to a psychosocial stressor). Differences between two phases are interpreted as changes in the EEG measure due to the presence of a psychosocial stressor. An overview of the phase-specific comparisons which have been used in the meta-analyses is shown in Figure 3. For two articles, multiple phase comparisons were possible (see Figure 3). Only one comparison from each study was included to not introduce possible biases in the meta-analysis that might have been present in the study. For the article by Betti and colleagues (2017),

we chose to include the baseline-recovery comparison since both phases report data from resting-state EEG, which is not the case with the baseline-reactive comparison. For the study by Wang and colleagues (2015), we chose to include the baseline-anticipatory comparison, since both phases report data from resting-state EEG, which is not the case with the baseline-reactive comparison. The decision to include the baseline-anticipatory instead of the baseline-recovery comparison was made because the baseline phase is closer to the anticipatory phase compared to the recovery phase in time. One article by Izhar et al. (2019) contained theta power values and thus was eligible for the meta-analysis but was not included since the reactive phase was compared to a baseline recording. Since participants were engaged with a task in the reactive phase, differences between this phase and the resting-state baseline recording to which the obtained EEG data was compared, could not be uniquely attributed to the presence of a psychosocial stressor.Whereas the comparison of two phases within an article makes it possible to investigate the influence of psychosocial stress in the different phases of the stress response, a considerable amount of variability is still present between the articles that are included in the meta-analyses. Therefore, it is likely that the reported results are not only representative of the underlying effect of psychosocial stress but are also influenced by other factors as well, resulting in possible differences regarding reported results and effect sizes. For these reasons, a random effects model is chosen to perform the meta-analyses, since random effects models in meta-analyses do not assume statistical homogeneity or a common effect size between included studies (Tufanaru et al., 2015). To assess possible publication bias, funnel plots are generated, and the Egger's test is conducted to assess funnel plot asymmetry (Egger et al., 1997; Sterne et al., 2011). The generation of the funnel plots and subsequent Egger's tests are conducted in R (version 4.1.1). The complete analysis can be found in the supplementary materials (section 7.6.6.) and the R files can be found on GitHub. No subgroup analyses are conducted regarding the specific stressor phases due to the limited number of included articles. To correct for small samples, which tend to overestimate effect sizes, Hedges' g is used for effect size calculation. The meta-analyses were conducted using Review Manager (RevMan), version 5.4.1 (Review Manager (Revman), 2012). The MATLAB code used for data pooling as well as the final RevMan file containing the meta-analytic results can be found on GitHub.

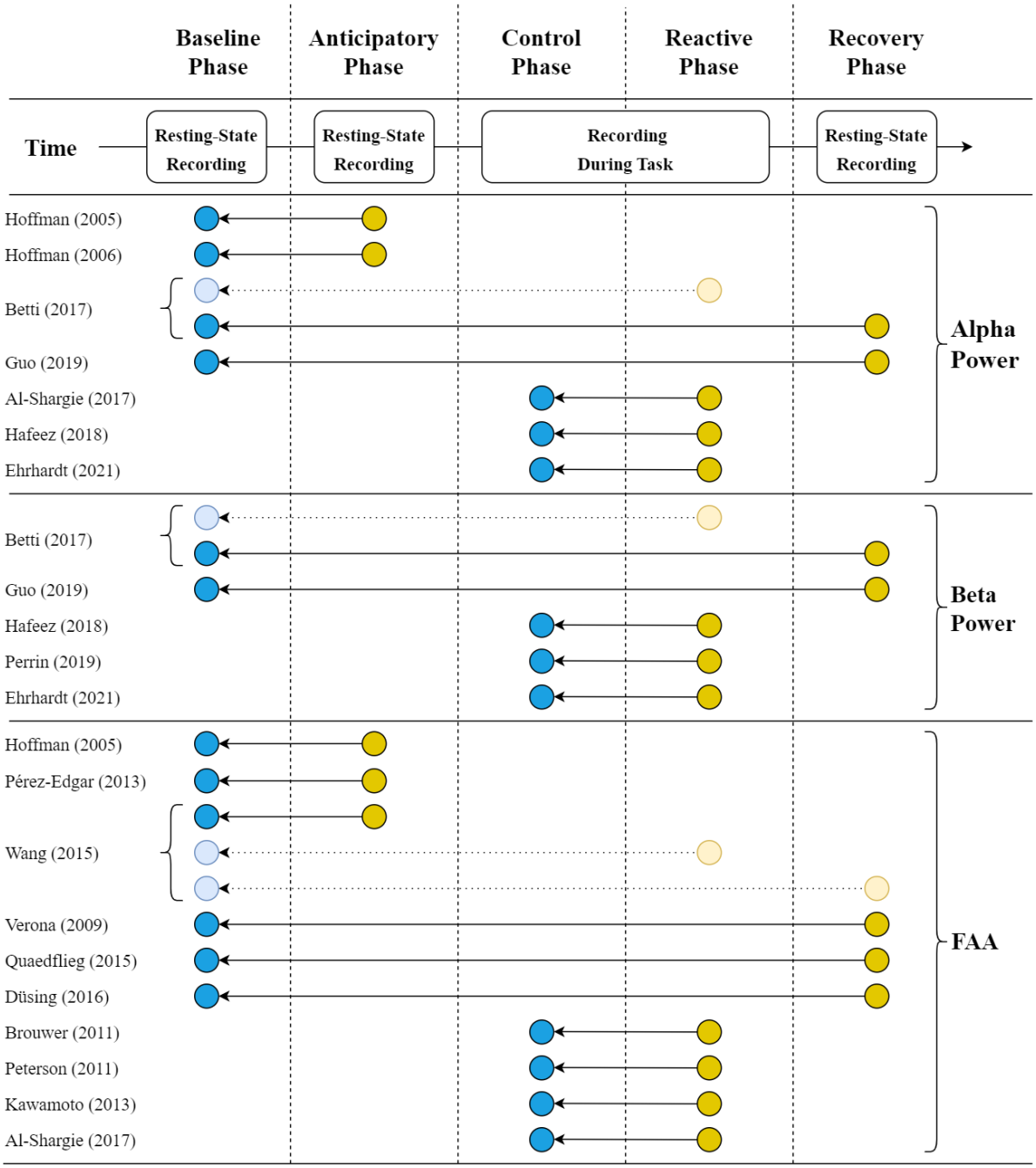

Figure 3: Figure showing which data from each article is used in the meta-analyses. **Top part of the figure**: identification of the different phases which can be present in each article. **Middle part of the figure**: identification of the type of EEG data which is collected during the corresponding phase and the occurrence of the different phases with respect to time. Resting-state recording: indicates that during this phase, resting-state EEG data is collected. Recording during task: indicates that during this phase, EEG data is recorded while a participant is actively engaged with a task. **Lower part of the figure**: shows which data from each article is used in the meta-analysis. A blue circle denotes data used in the meta-analysis from a phase in which no psychosocial stressor is present. These phases are either the baseline phase or the control phase. A yellow circle denotes data used in the meta-analysis from a phase in which a psychosocial stressor is present or a phase where the effects of a psychosocial stressor are still present. These phases are either the anticipatory phase, the reactive phase or the recovery phase. An arrow indicates the comparison made between the data from the phase in which a psychosocial stressor is present and the phase without a psychosocial stressor. A light blue/yelow circle indicates that the corresponding article contains data from the indicated phases, but that this data is not used in the meta-analysis. The articles are defined on the left of the figure, and are grouped based on the EEG measure on which a meta-analysis is conducted (indicated at the right of the figure). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Results

3.1. Search Results

After deduplication of the articles, a total of 9088 publications were pinpointed as potentially relevant (3427 from PubMed, 3571 from Web of Science, 6152 from Embase and 10 from reference lists of publications). After abstract review, 8892 publications were excluded, leaving 196 articles for full text review. After a full text review, 162 publications were excluded, leaving 34 articles suitable for this systematic review. From these 34 articles, 7 were identified as reporting from the same population (Subhani et al., 2013, 2016a,b): and (Al-Shargie et al., 2016; 2017a; 2017b, 2018). Therefore, the 34 articles selected for this systematic review report on 29 distinct participant populations (n = 1213, age range = 18–50 years, the characteristics of the studies are presented in Table 1).

Table 1. Demographics, investigated neural activity, employed stressor paradigm, employed phase comparison, employed EEG measure, and employed frequency ranges of the included articles. **Legend**: *Ppts* = Participants; *M* = Mean; *STD* = Standard Deviation; *Activity* = type of neural activity which is investigated; *Induced* = task-induced neural activity; *Evoked* = task-evoked neural activity; *Paradigm* = employed psychosocial stressor; *MIST* = Montreal Imaging Stress Task (Dedovick et al., 2005); *MAST* = Maastricht Acute Stress Test (Smeet et al., 2012); *SET* = paradigms employing social-evaluative threat as stressor; *TSST* = Trier Social Stress Test (Kirschbaum et al., 1993); *Cyberball* = Cyberball paradigm (Williams et al., 2000); *SJP* = Social Judgment Paradigm (van der Molen et al., 2017); *SPT* = Social Performance Task (Harrewijn et al., 2016); *Anticipation* = Anticipatory phase; *Reactive* = Reactive Phase; *Recovery* = Recovery phase; *Baseline* = Baseline Recording; *Measure* = The EEG measure used in the article; A_{pow} = Alpha Power; B_{pow} = Beta Power; T_{pow} = Theta Power; D_{pow} = Delta Power; S_{pow} = Sigma Power; *FAA* = Frontal Alpha Asymmetry; *RG* = Relative Gamma; *SR* = Slowing Ratio; *AAC* = Alpha Attenuation Coefficient; *dPAC* = Debiased Phase-Amplitude Coupling; *AAC* = Amplitude-Amplitude Correlation; *PR* = Theta-Alpha Power Ratio. δ = delta ; θ = theta ; α = alpha ; σ = sigma ; β = beta ; γ = gamma. (↓) = Significant decrease; (↑) = Significant increase; (-) = insignificant change; *FR* = Frequency ranges used in the article. [1] = Subhani, A.R., Malik, A.S., Kamil, N., & Saad, M. N. M. [2] = Subhani, A. R., Malik, A. S., Kamil, N., Naufal, M., & Saad, M. N. M.

Note: the current table is slightly adjusted for visual representation. No alterations were made to the content.

Author (Year)	Ppts (tot, male)	Age (M, STD)	Activity	Paradigm	Stress Phase	No-Stress Phase	Measure	FR (Hz)
Al-Shargie (2016)	22 (22)	26 (4)	Induced	MIST	Reactive	Control	A_{pow} (↓) B_{pow} (-)	α : 8 – 12.5 β : 12.5 - 30
Al-Shargie (2017b)	25 (25)	22 (3)	Induced	MIST	Reactive	Control	A_{pow} (↓)	α : 8 - 13
Al-Shargie (2017a)	22 (22)	22 (2)	Induced	MIST	Reactive	Control	A_{pow} (↓)	α : 8 - 16
Al-Shargie (2018)	18 (18)	-	Induced	MIST	Reactive	Control	A_{pow} (↓) FAA (↓)	α : 8 - 16
Betti (2017)	12 (8)	40.8 (9.5)	Induced	MAST	Reactive Recovery	Baseline Baseline	A_{pow} (↑) B_{pow} (-) A_{pow} (↓) B_{pow} (-)	α_1 : 8 – 9 α_2 : 10 – 12 β_1 : 13 – 17 β_2 : 18 - 30
Brouwer (2011)	9 (6)	-	Induced	SET	Reactive	Control	FAA (-)	α : 8 - 13

Crost (2008)	89 (89)	24.2	Induced	SET	Reactive	Control	FAA (-)	α : 8- 10.25
Düsing (2016)	49 (17)	22.5 (3.33)	Induced	TSST	Recovery	Baseline	FAA (↑)	α : 8 - 13
Ehrhardt (2021)	34 (19)	25.8 (6)	Induced	SET	Reactive	Control	A_{pow} (-) B_{pow} (-)	α : 8 – 13 β : 13 - 30
Guo (2020)	150 (75)	23.8 (1)	Induced	TSST	Recovery	Baseline	A_{pow} (↓) B_{pow} (↑)	α_{low} : 8 – 10 α_{high} : 10 – 12 β_{low}: 12 – 20 β_{high}: 20 - 30
Hafeez (2018)	14 (11)	-	Induced	MIST	Reactive	Control	T_{pow} (↓) A_{pow} (↓) B_{pow} (↑)	θ : 4 – 8 α : 8 – 16 β : 16 - 31
Hofmann (2005)	27 (27)	19 (1.3)	Induced	TSST	Anticipation	Baseline	A_{pow} (↓) FAA (-)	α : 8 – 13
Hofmann (2006)	32 (0)	18.5 (0.7)	Induced	TSST	Anticipation	Baseline	A_{pow} (↓)	α : 8 - 13
Izhar (2019)	8 (8)	19.5 (0.8)	Induced	TSST	Reactive	Baseline	B_{pow} (↑)	β : 13 - 30
Minguillon (2016)	6 (-)	26.3 (6.4)	Induced	MIST	Reactive Recovery	Control Control	T_{pow} (↓) A_{pow} (↓) FAA (↓) B_{pow} (↑) RG (↑)	θ : 4 – 7 α : 8 – 13 β : 14 – 24 γ : 25 - 45
Minguillon (2017)	6 (-)	25.3 (4.8)	Induced	MIST	Reactive	Recovery	RG (↑)	θ : 4 – 7 α : 8 – 13 γ : 25 - 45
Kawamoto (2013)	19 (8)	18.3 (-)	Induced	Cyberball	Reactive	Control	FAA (-)	α : 8 - 13
Kortdink (2018)	65 (0)	19.7 (1.5)	Evoked	SJP	Reactive	Control	T_{pow} (↑)	θ : 4 - 8
Papousek (2019)	62 (12)	24 (4)	Induced	TSST	Anticipation Recovery	Baseline	FAA (-)	α : 8 - 12
Perrin (2019)	24 (24)	26.5 (4)	Induced	TSST	Recovery	Recovery	D_{pow} (↓) T_{pow} (↑) SR (↓) AAC (↓) S_{pow} (-) B_{pow} (↑)	δ : 0.5 – 4.5 θ : 4.5 – 8 α : 8 – 12 σ : 13 – 15 β : 15 - 32
Peterson (2011)	40 (20)	-	Induced	Cyberball	Reactive	Control	FAA (-)	α : 10.25 – 12.5
Pérez-Edgar (2013)	45 (19)	21.1 (5.3)	Induced	TSST	Anticipation	Baseline	FAA (-)	α : 8 - 13
Poppelaars (2018)	HSA: 20 (52) LSA: 32 (52)	19.7 (1.5) 20 (1.6)	Induced	SPT	Anticipation Recovery	Baseline	dPAC (-) AAC (-)	δ : 1 – 4 β : 14 - 30
Poppelaars (2021)	64 (34)	M:22.4(2.6) F: 22.9 (2.8)	Induced	SPT	Anticipation Recovery	Baseline	dPAC (-) AAC (-)	δ : 1 – 4 β : 14 - 30
Quaedflieg (2015)	70 (30)	20.8 (2.7)	Induced	MAST	Recovery	Baseline	FAA (-)	α : 8 - 13
Subhani (2013)	10 (10)	-	Induced	MIST	Reactive Recovery	Control Baseline	PR (↑)	θ : 4 – 8 α : 8 - 12

Subhani (2016) [1]	22 (-)	-	Induced	MIST	Reactive	Control	Coherence (↑,↓)	α : 8 – 12 β : 13 - 30
Subhani (2016) [2]	22 (-)	22 (1.5)	Induced	MIST	Recovery	Baseline	Coherence (↑,↓)	α : 8 – 12 β : 13 - 25
van der Veen (2016)	194 (48)	20.9 (2.3)	Evoked	SJP	Reactive	Control	T_{pow} (↑) D_{pow} (↓)	δ : 2 – 3 θ : 5 – 7
Vaquero- Blasco (2020)	17 (-)	24.2 (4)	Induced	MIST	Reactive Recovery	Control	RG (↑) RG (↓)	θ : 4 – 8 α : 8 – 13 γ : 25 - 45
Vaquero- Blasco (2021)	19 (8)	22.7 (5.5)	Induced	MIST	Reactive Recovery	Control Reactive	RG (↑) RG (↓)	θ : 4 – 8 α : 8 – 13 γ : 25 - 45
Verona (2009)	43 (-)	24.6 (6.5)	Induced	SET	Recovery	Baseline	FAA (-)	α : 8 - 13
Wang (2015)	25 (13)	23.1 (2.2)	Induced	TSST	Anticipation Reactive Recovery	Baseline	FAA (↓) FAA (↓) FAA (-)	α : 8 - 12
Yao (2020)	HPS: 50 (23) LPS: 50 (29)	20.4 (0.3) 20.2 (0.3)	Evoked	Cyberball	Reactive	Control	D_{pow} (↑) T_{pow} (↑) A_{pow} (↓)	δ : 1 – 4 θ : 4 – 8 α : 7 – 13

3.2. Quality assessment and analysis of bias

The results of the quality assessment and analysis of bias are shown in Table 2. The average score from the risk of bias analysis is 74.47% (standard deviation = 9.95; minimum = 57%; maximum = 93%), showing a high variability in the final scores. Overall, all articles precisely describe their research questions and hypotheses (question one) and that almost all articles employ an appropriate study design (question two). Large differences however are found in the description of the demographic information of the sample population (question three), the explanation of the blinding of the participants (question seven), the estimate of variance (question 11) and the control of confounding factors (question 12). It is notable that most articles scored poorly on question nine, indicating that small sample sizes were common across the studies. One article did not include any information, 32 out of the 34 included articles scored "partial" (= 1, see above) and one article included all information on question 10. The extended risk of bias analysis with answers to the subquestions eight and ten can be found in the supplementary materials (section 7.6.2.). It should be noted that the research questions of this systematic review do not always align with the research questions posed in the articles. This can lead to lower scores for multiple articles regarding questions such as the reporting of statistical analysis (question ten c) or the estimation of variance (question 11).

Table 2: Risk of Bias analysis. To obtain the percentage score, the total score was divided by 28 (= 14*2) and multiplied by 100.

Author (Year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total	Percentage
Al-Shargie (2016)	2	2	0	2	2	2	1	2	0	1	0	2	1	1	18	64
Al-Shargie (2017)	2	2	0	2	2	2	1	2	0	1	1	2	2	2	21	75
Al-Shargie (2017)	2	2	0	2	2	2	1	1	0	1	0	1	2	2	18	64
Al-Shargie (2017)	2	2	0	1	2	2	1	2	0	1	2	1	1	1	18	64
Betti (2017)	2	2	2	2	2	2	1	1	0	0	2	1	2	1	20	71
Brouwer (2011)	2	1	1	1	2	2	2	2	0	1	1	1	2	1	19	68
Crost (2008)	2	1	1	1	1	2	1	2	2	1	1	1	2	2	20	71
Düsing (2016)	2	2	2	2	2	2	1	2	1	2	2	1	2	2	25	89
Ehrhardt (2021)	2	2	0	2	2	2	1	2	1	1	2	1	2	2	22	79
Guo (2019)	2	2	1	2	2	2	1	1	2	1	2	1	1	2	22	79
Hafeez (2017)	2	2	1	1	2	2	1	2	0	1	1	1	2	1	19	68
Hofmann (2005)	2	2	2	2	2	2	2	2	0	1	1	1	2	2	23	82
Hofmann (2006)	2	2	2	2	2	2	1	1	0	1	1	1	2	2	21	75
Izhar (2019)	2	2	1	2	2	2	1	2	0	1	2	1	2	2	22	79
Kawamoto (2013)	2	2	0	1	2	2	0	2	0	1	1	1	2	2	18	64
Kortdink (2018)	2	2	1	2	2	2	2	2	1	1	0	1	2	2	22	79
Minguillon (2016)	2	2	0	1	2	2	1	1	0	1	0	1	2	2	17	61
Minguillon (2017)	2	2	1	1	2	2	1	1	0	1	0	1	2	2	18	64
Papousek (2019)	2	2	1	2	2	2	2	2	2	1	0	2	2	2	24	86
Pérez-Edgar (2013)	2	2	2	2	2	2	1	1	1	1	2	1	2	2	23	82
Perrin (2019)	2	1	1	2	2	2	2	1	0	1	2	1	1	2	20	71
Peterson (2011)	2	2	2	1	2	2	2	1	0	1	2	1	2	2	22	79
Poppelaars (2018)	2	2	2	2	2	2	2	2	2	1	2	1	2	2	26	93
Poppelaars (2021)	2	2	1	2	2	2	1	2	2	1	2	1	2	2	24	86
Quaedflieg (2015)	2	2	1	2	2	2	2	2	2	1	2	1	2	2	25	89
Subhani (2013)	2	2	0	1	2	2	1	2	0	1	2	1	1	2	19	68
Subhani (2016) [(1)]	2	2	0	0	2	2	1	2	0	1	0	1	2	1	16	57
Subhani (2016) [(2)]	2	2	1	1	2	2	1	2	0	1	0	1	1	1	17	61
van der Veen (2016)	2	2	1	2	2	2	1	2	2	1	1	1	2	2	23	82
Vaquero-Blasco (2020)	2	2	0	1	2	2	1	2	0	1	0	1	2	2	18	64
Vaquero-Blasco (2021)	2	2	1	2	2	2	1	1	0	1	0	1	1	2	18	64
Verona (2009)	2	2	1	2	2	2	2	2	1	1	2	1	2	2	24	86
Wang (2015)	2	2	2	2	2	2	1	2	2	1	2	1	2	2	25	89
Yao (2020)	2	2	0	2	2	2	2	2	2	1	0	1	2	2	22	79

3.3. Systematic review

The results of the articles included in this systematic review will be discussed with a focus on which stress phase was investigated and how the measured EEG variable changed due to the presence of an acute psychosocial stressor. All results are discussed by making a comparison between a phase where a psychosocial stressor is present (*anticipatory*, *reactive* or *recovery* phase) and a phase without the presence of a psychosocial stressor (a *baseline recording* at the start of the study or a *control condition* where participants perform the same task as during the reactive phase, but without the presence of a psychosocial stressor). The anticipatory and recovery phase are compared to a baseline condition if possible since EEG data from both stress response phases is resting-state data, which is also the case for a baseline recording. The reactive phase is compared to a control condition and not a baseline recording, if possible, since differences between a baseline recording and EEG data recorded during the reactive phase can not only be attributed to the psychosocial stressor, but also to the task which is performed during the reactive phase. An overview of the stress response phases which are investigated (*Stress Phase* column) and the phases without psychosocial stressors to which they are compared (*No-Stress Phase* column), as well as the type of neural activity which is investigated (*Activity* column), employed psychosocial stressor (*Paradigm* column), investigated EEG measure and reported findings (*Measure* column) and specific frequency ranges (*FR* column) can be found in Table 1. Three types of results have been identified in the included articles: spectral power features, spectral power derived features, and functional connectivity features. Spectral power features are calculated by obtaining the power spectral density, usually through a Fourier transformation, and selecting a frequency band of interest to calculate the average power within it (Cohen, 2014). Spectral power derived features use spectral power measures for their calculation but combine multiple power values from distinct spatial locations or different frequency ranges. Functional connectivity features investigate temporal dependencies between spatially distinct neurophysiological events and give insight into the communicational mechanics of the brain (Friston, 1994). Results are grouped by the type of EEG feature, namely power, power-derived and functional connectivity features. The employed psychosocial stress paradigms are not discussed, unless necessary to understand the results, but can be found in Table 1. When discussing results, “significant” is defined as statistically significant ($p < 0.05$) after multiple comparison correction (if applied in the article itself).

3.3.1. Power features

3.3.1.1. Delta power

In three articles, delta power was employed as a measure to investigate psychosocial stress. van der Veen and colleagues (2016) investigated the reactive phase by employing the social judgment paradigm (SJP), where participants need to guess whether other participants would like or dislike them after seeing a picture of them and afterwards receive the corresponding, computer-generated, feedback. This paradigm leads to four possible conditions: expected or unexpected acceptance/rejection, and the delta power has been calculated from the corresponding ERP segments (Somerville et al., 2006). They found a significantly decreased delta power when participants were rejected (expected or unexpected) or unexpectedly accepted compared to the expected acceptance condition. This effect was the only significant effect and was found at electrode FCz. Yao et al. (2020) also employed the social judgment paradigm and found that delta power was increased when participants experienced feedback in a social context (reactive phase) compared to a nonsocial context (control condition). Perrin et al. (2019) looked at the delta frequency band (electrodes Fz, C3, C4, Cz, Pz, Oz) throughout the day after a public speaking task in the morning (recovery phase). They found that the delta power was significantly lower after this speaking task compared to a control condition (i.e., no speaking task in the morning).

3.3.1.2. Theta power

In six articles, results regarding theta power are reported. In three articles, task-evoked neural activity in the reactive phase was investigated during the SJP (see section 3.3.1. for clarity) (Somerville et al., 2006). In two articles, significantly increased theta power during the unexpected rejection condition compared to the other conditions was reported (Kortink et al., 2018; van der Veen et al., 2016), whereas in the third article an overall increase in theta power during social feedback was reported (reactive phase) compared to a control condition (Yao et al., 2020). Minguillon et al. (2016) investigated the reactive and recovery phase and found that theta power was decreased during the reactive phase when compared to both a control condition or the recovery phase. This decrease in theta power during the reactive phase compared to a control condition was also found by Hafeez et al. (2018). Perrin et al. (2019) investigated the recovery phase and found that theta power was significantly higher when compared to the recovery phase of a control condition.

3.3.1.3. Alpha power

In twelve articles, alpha power changes from (mainly) the frontal electrodes are reported (Al-Shargie et al., 2016, 2017a, 2017b, 2018; Betti et al., 2018; Ehrhardt et al., 2021; Guo et al., 2019; Hafeez et al., 2018; Hofmann, 2006; Hofmann et al., 2005; Minguillon et al., 2016; Yao et al., 2020). In eight articles, the reactive phase, compared to a control condition, was investigated and seven times a significant decrease in alpha power during the reactive phase (Al-Shargie et al., 2016, 2017a, 2017b, 2018; Hafeez et al., 2018; Minguillon et al., 2016; Yao et al., 2020) was found. In one article however, a nonsignificant drop in alpha power between the reactive phase (when participants perform the paced auditory serial addition task (PASAT, Gronwall & Sampson, 1974) with time constraint and social feedback) and a control condition (PASAT with only a time constraint) was found (Ehrhardt et al., 2021). In one article the reactive phase was compared to a baseline recording instead of a control condition and an increase in alpha power during the reactive phase was found, which is contrary to all other articles in which alpha power was employed (Betti et al., 2018). The anticipatory phase, compared to a baseline recording, was investigated in two articles and a significant reduction in alpha power during the anticipatory phase was found in both articles (Hofmann, 2006; Hofmann et al., 2005). Finally, in two articles results from the recovery phase, compared to a baseline recording, were reported and here a significant decrease in alpha power during this phase of the psychosocial stress response was found (Betti et al., 2018; Guo et al., 2019).

3.3.1.4. Sigma power

One article investigated the influence of psychosocial stress on sleep quality and investigated if sigma power (13–15 Hz) was affected during the recovery phase (Perrin et al., 2019). Sigma power, linked with sleep quality of sleeping individuals (Spiegelhalder et al., 2012), was not significantly affected by psychosocial stress in the recovery phase.

3.3.1.5. Beta power

Beta power variations due to psychosocial stress were investigated in eight articles, which report results from the reactive and recovery phase (Al-Shargie et al., 2016; Betti et al., 2018; Ehrhardt et al., 2021; Guo et al., 2019; Hafeez et al., 2018; Izhar et al., 2019; Minguillon et al., 2016; Perrin et al., 2019). In five articles, the reactive phase was compared to a control condition (Al-Shargie et al., 2016; Ehrhardt et al., 2021; Hafeez et al., 2018; Minguillon et al., 2016; Perrin et al., 2019). Hafeez et al. (2018) as well as Perrin et al. (2019) reported significantly higher beta power during the reactive phase. Al-Shargie et al. (2016) also reported

higher beta power during the reactive phase, but this difference was not significant. Minguillon et al. (2016) reported a significantly higher beta power during the reactive phase compared to the recovery phase for both prefrontal (Fp1, Fp2) and frontal (Fz, F3, F4, F7, F8) electrodes. When compared to a control condition, the beta power is significantly higher during the reactive phase, but only at the frontal electrodes. Ehrhardt et al. (2021) reported, contrary to other articles investigating the reactive phase - control condition difference, a decrease in beta power during the reactive phase, although this difference is nonsignificant. In two articles, the reactive phase was also investigated, but was compared to a baseline recording instead of a control condition (Betti et al., 2018; Izhar et al., 2019). Izhar et al. (2019) reported a significant increase in beta power during the reactive phase, whereas Betti et al. (2018) reported a reduction in beta power, although this was not significant. Finally, in two articles results from the recovery phase, compared to a baseline recording were described (Betti et al., 2018; Guo et al., 2019). Guo et al. (2019) reported a significant increase in beta power during the recovery phase, whereas Betti et al. (2018) reported an insignificant increase.

3.3.2. Power-derived features

3.3.2.1. Slowing ratio

In one paper, the slowing ratio (an EEG measure reflecting cortical arousal during sleep, defined as the ratio of the power in the slower (delta, theta, 0.5–8Hz) frequency ranges by the power of the faster (alpha, sigma, beta, 12–32Hz) ranges (D'Rozario et al., 2013)) measured during the recovery phase was significantly lower after the psychosocial stress exposure compared to a control condition (Perrin et al., 2019)

3.3.2.2. Theta-alpha power ratio

Subhani et al. (2013) used theta-alpha power ratio (an index reflecting the internal and external load on an individual, defined as the ratio of the theta power value at electrode Fz by the alpha power value at electrode Pz (Holm et al., 2009)) in both the reactive and recovery phase. In the reactive phase, they found that the theta-alpha power ratio was significantly higher during the stress condition compared to the control condition. This difference did not persist in the recovery phase.

3.3.2.3. Relative gamma

In four papers, relative gamma (RG, an index initially identified in research regarding meditation and defined as the ratio of gamma band power by the average power of the combined theta and alpha band (Lutz et al., 2004; Steinhubl et al., 2015)) was used. Minguillon and colleagues (2016, 2017) investigated RG during the reactive and recovery phase (2016) and during the recovery phase (2017) at the prefrontal (Fp1, Fp2), frontal (Fz, F3, F4, F7, F8), central (Cz, C3, C4) and parietal (Pz, T5, T6) electrodes. During the reactive phase, RG was significantly higher during the stress condition compared to the control condition for all electrode locations (Minguillon et al., 2016). During the recovery phase, relative gamma decreased significantly compared to the reactive phase, again for all electrode positions (Minguillon et al., 2016, 2017). Vaquero-Blasco and colleagues (2020, 2021) reported alterations in RG during the reactive and recovery phase. RG decreased from the reactive to the recovery phase, although it is not clear whether this was significant or not due to the specific research question of the studies and corresponding absence of relevant p-values.

3.3.2.4. Frontal alpha asymmetry

Frontal Alpha Asymmetry (FAA) is computed by obtaining the natural log transformed power in the alpha frequency band from two frontal EEG electrodes that are opposite symmetric compared to the midline (mostly F3/F4 or F7/F8) and subtracting the power value of the left electrode from the right (see formula 3). FAA reflects approximately the relative difference between the alpha power of the frontal part of the left and right hemisphere, and a positive FAA value indicates a relative greater alpha power of the right frontal hemisphere. Changes in FAA are believed to denote emotional or motivational responses of an individual whereby an increase in FAA (indicating an increase of relative right hemispheric activity) likely indicates more withdrawal-related states (Smith et al., 2017).

$$FAA = ln\big(P_{\alpha}(right)\big) - ln\big(P_{\alpha}(left)\big) \qquad (3)$$

In thirteen articles, FAA was used to investigate the various phases of the psychosocial stress response (Al-Shargie et al., 2018; Brouwer et al., 2011; Crost et al., 2008; Düsing et al., 2016; Hofmann et al., 2005; Kawamoto et al., 2013; Minguillon et al., 2016; Papousek et al., 2019; Pérez-Edgar et al., 2013; Peterson et al., 2011; Quaedflieg et al., 2015; Verona et al., 2009; Wang et al., 2015). In four articles, the anticipatory phase, compared to a baseline recording, was investigated (Hofmann et al., 2005; Papousek et al., 2019; Pérez-Edgar et al., 2013; Wang et al., 2015). In three articles a decrease in FAA was reported, one significant (Wang

et al., 2015), and two insignificant (Hofmann et al., 2005; Pérez-Edgar et al., 2013). Papousek et al. (2019) however, reported an increase in the laterality coefficient (which can be understood as a normalized version of FAA) but these results were also insignificant. In seven articles the reactive phase was investigated. In six articles, it was compared to a control condition (Al-Shargie et al., 2018; Brouwer et al., 2011; Crost et al., 2008; Kawamoto et al., 2013; Minguillon et al., 2016; Peterson et al., 2011), whereas in one article it was compared to a baseline recording (Wang et al., 2015). In four articles, a decrease in FAA was reported during the reactive phase compared to either a control condition or a baseline recording, three times significant (Al-Shargie et al., 2018; Minguillon et al., 2016; Wang et al., 2015), and one time insignificant (Kawamoto et al., 2013). Twice an increase in FAA during the reactive phase was reported, but neither were significant (Brouwer et al., 2011; Peterson et al., 2011). In one article the participant population was divided by anxiety and defensiveness scores, so an overall result of FAA changes is not present (Crost et al., 2008). Finally, in four articles the recovery phase, compared to a baseline recording was investigated (Düsing et al., 2016; Quaedflieg et al., 2015; Verona et al., 2009; Wang et al., 2015). In three articles, small increases in FAA were reported, but aside from the results of electrode pair F3/F4 from Düsing et al. (2016), no results were significant (Düsing et al., 2016; Quaedflieg et al., 2015; Verona et al., 2009). In one article, no change at all between baseline and recovery was found (Wang et al., 2015). Aside from frontal alpha asymmetry, 3 articles also reported alpha asymmetry results, but from the parietal regions (Crost et al., 2008; Hofmann et al., 2005; Pérez-Edgar et al., 2013). Hofmann et al. (2005) as well as Pérez-Edgar et al. (2013) investigated the anticipatory phase, compared to a baseline recording, and neither found a significant result. Crost et al. (2008) investigated the reactive phase, compared to a control condition, and found no significant results.

3.3.2.5. Alpha attenuation coefficient

In one paper, the alpha attenuation coefficient (AAC, an index of sleepiness and defined as the division of the mean alpha power during an eyes-closed resting state recording by the mean alpha power during an eyes-open resting state recording (Stampi et al., 1995)) was used and a significant lower AAC during the recovery phase when participants were exposed to a psychosocial stressor compared to the recovery after a control condition was found (Perrin et al., 2019).

3.3.3. Functional connectivity features

3.3.3.1. Coherence

In two articles, reporting results of the same experiment and population, coherence (a FC measure that infers the similarity between the power spectra of two time series and can roughly be understood as the frequency equivalent of cross-correlation (Cohen, 2014)) was used to investigate psychosocial stress-related brain activity alterations. Subhani et al. (2016a) reported the results of the reactive phase of the stress response compared to a control condition and found increased coherence within the left and right frontal central electrode clusters as well as decreased coherence between both clusters in the delta band, increased coherence mainly between the right fronto-central electrodes in the theta band, increased coherence mainly between the prefrontal, frontal and central electrodes in the alpha band and increased coherence between the frontal, central and temporal/parietal electrodes in the beta band. Subhani et al. (2016b) compared the stress recovery phase to a baseline recording collected before the start of the experiment and found decreased coherence mainly between the right frontal and central electrodes in the delta band, decreased coherence mainly between the occipital, temporal, parietal and right frontal electrodes as well as increased coherence between the prefrontal and left central electrodes in the theta band, some decreased coherence between occipital electrodes in the alpha band and increased coherence between the Pz electrode and frontal and prefrontal electrode in the beta band. It should be noted that the coherence between all electrodes (19 in total) and within multiple frequency bands had been calculated and that the results were not corrected for multiple comparisons, so these results should be interpreted with caution.

3.3.3.2. Phase-amplitude coupling & amplitude-amplitude correlation

Poppelaars and colleagues (2018, 2021) used both phase-amplitude coupling (a FC measure investigating the relationship between the phase of an EEG signal in a low frequency band with the amplitude of an EEG signal in a high frequency band (Tort et al., 2010)) and amplitude-amplitude correlation (a FC measure investigating the relationship between the amplitudes of EEG signals in different frequency ranges (Knyazev, 2011)) between the delta and beta band (Poppelaars et al., 2018, 2021). They investigated the anticipatory and recovery phase but found no significant effects due to the psychosocial stressor using either the phase-amplitude coupling or the amplitude-amplitude correlation.

3.4. Meta-analytic results

3.4.1. Alpha power

From the 12 articles in which results regarding alpha power changes were reported, five articles were omitted from further meta-analysis. In four articles, results from the same population were reported (Al-Shargie et al., 2016; 2017a; 2017b, 2018), so the article reporting results from the largest population was included in the meta-analysis (Al-Shargie et al., 2017b), whereas the other three were discarded (Al-Shargie et al., 2016; 2017a, 2018). Two articles were omitted as it was not possible to extract the results (Minguillon et al., 2016; Yao et al., 2020). Therefore, seven articles are included in the meta-analysis (Al-Shargie et al., 2017a, 2017b; Betti et al., 2018; Ehrhardt et al., 2021; Guo et al., 2019; Hafeez et al., 2018; Hofmann, 2006; Hofmann et al., 2005). As mentioned in section 2.5., the article from Betti et al. (2018) investigated alpha power in both the reactive and recovery phase. Since the EEG data from both phases is compared with a baseline, resting-state recording at the start of the experiment, results from the recovery phase are chosen for the meta-analysis, since resting-state data is also recorded in this stage, which is not the case in the reactive phase (see Figure 3). Interestingly, the result of the reactive phase from Betti et al. (2018) reports a small to moderate negative effect size (hedge's $g = -0.23$) and is the only negative effect size (which can be understood as an increase in alpha power) of all articles included in the alpha power meta-analysis. Figure 4 shows the details regarding the alpha power meta-analysis. Overall, a significant effect was found (SMD = 0.6; [0.24, 0.96]; Z = 3.30; p = 0.001), showing that alpha power significantly decreases due to psychosocial stress, regardless of the stress phase which was investigated. Heterogeneity tests show that high heterogeneity is present in the meta-analysis ($I2 = 68\%$; p = 0.005). Due to the limited amount of included studies, no further subgroup analysis can be performed to further investigate the reasons for this heterogeneity, but the low number of articles as well as the low number of participants in multiple studies might be the reason. Analyses suggest that no publication bias is present (p = 0.336, see section 7.6.6.).

3.4.2. Beta power

From the eight articles in which beta power results are described, five articles were included in the meta-analysis (Betti et al., 2018; Ehrhardt et al., 2021; Guo et al., 2019; Hafeez et al., 2018; Perrin et al., 2019). Three articles were omitted, two due to the absence of data or figures (Al-Shargie et al., 2016; Minguillon et al., 2016) and one due to the fact that the reactive phase (EEG data during a task) was investigated, whereas only a baseline, resting-state EEG

recording was present for comparison (Izhar et al., 2019). Similarly to the alpha power meta-analysis, Betti et al. (2018) report results from both the reactive and recovery phase. To eliminate bias in the meta-analysis, only one result was chosen to be included and, similarly to the alpha power meta-analysis, we chose to include the result reporting changes in the recovery phase (see section 2.5. and Figure 3). The effect size reported by Betti et al. (2018) for the reactive phase compared to the baseline recording is small (hedge's g = 0.14), showing a small decrease in overall beta power during the reactive phase compared to the baseline measurement. Figure 5 shows the details regarding the beta power meta-analysis. Overall, no significant effect was found (SMD = − 0.31; [− 0.88 0.27]; Z = 1.05; p = 0.29), meaning that beta power did not change significantly from a non stressed condition to a psychosocially stressed condition. Due to the limited number of articles included in the meta-analysis, no further subgroup analysis can be performed. Heterogeneity tests show that high heterogeneity is present (I2 = 80%; p = 0.0001). Similarly to the alpha power meta-analysis, the low amount of results combined with the small sample size is likely the reason for this heterogeneity. The Egger's test indicated that no publication bias is present (p = 0.13, see section 7.6.6.). However, due to the low number of included studies, this result should be interpreted with caution since the Egger's test might lack sufficient power to correctly identify publication bias (Sterne et al., 2011).

3.4.3. Frontal alpha asymmetry

From the thirteen articles in which FAA results are reported, 10 articles are eligible for concurrent meta-analyses. Three articles were omitted from the analysis due to the absence of data or figures (Crost et al., 2008; Minguillon et al., 2016; Papousek et al., 2019). Two meta-analyses have been run for FAA, since FAA can be calculated for multiple electrode pairs and results from two electrode pairs, the F3/F4 and F7/F8 pairs, were commonly reported. Therefore, a meta-analysis has been conducted for each of these electrode pairs. In each meta-analysis eight articles are included. In six articles, FAA results were reported for both electrode pairs (Al-Shargie et al., 2018; Brouwer et al., 2011; Düsing et al., 2016; Peterson et al., 2011; Quaedflieg et al., 2015; Wang et al., 2015). In two articles, the results for the F3/F4 electrode pair alone were reported (Hofmann et al., 2005; Pérez-Edgar et al., 2013), whereas results for only the F7/F8 electrode pair were reported in two other articles (Kawamoto et al., 2013; Verona et al., 2009). Wang et al. (2015) reported results from multiple phases (anticipatory, reactive, and recovery), so to avoid bias in the meta-analyses, only one result is included. We chose to include the results from the anticipatory phase as this phase lies closest to the baseline recording

in time, therefore making it the least likely to be affected by unknown influences introduced throughout time (see section 2.5. and Figure 3).

3.4.3.1. F3/F4 electrode pair

Figure 6 shows the details regarding the FAA meta-analysis for electrode pair F3–F4. Overall, no significant effect was found (SMD = − 0.01; [− 0.20 0.22]; Z = 0.09; p = 0.93), showing that over the various phases of the psychosocial stress response, FAA when calculated using frontal electrodes F3 and F4 does not change significantly. No subgroup analysis was performed as not enough articles are present in the meta-analysis. Heterogeneity tests indicate low heterogeneity (I2 : 32%, p = 0.17), indicating that the articles in this meta-analysis likely report the same effect. No publication bias was detected by the Egger's test (p = 0.15, see section 7.6.6.).

3.4.3.2. F7/F8 electrode pair

Figure 7 shows the details regarding the FAA meta-analysis for electrode pair F7–F8. Overall, no significant effect was found (SMD = − 0.02; [− 0.19 0.15]. Z = 0.21; p = 0.84), showing that FAA, calculated using electrodes F7 and F8, does not change consistently throughout the psychosocial stress response. Due to the low number of included studies, no subgroup analysis investigating the variations in FAA between the various phases were conducted. Heterogeneity tests showed no heterogeneity in this meta-analysis (I2 = 0%; p = 0.78). No publication bias was detected by the Egger's test (p = 0.54, see section 7.6.6.).

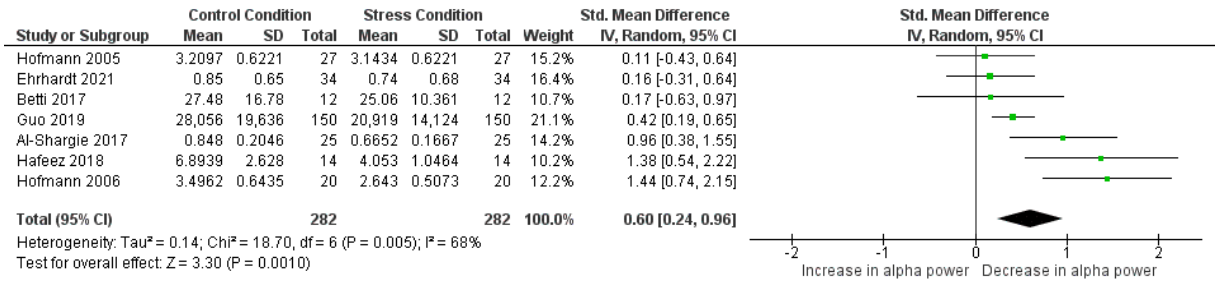

Figure 4. Forest plot illustrating the standardized mean differences (SMD), individual effect sizes, overall effect size and heterogeneity statistics for the meta-analysis examining changes in alpha power from a control (non-stressed) condition to a stress condition. Hofmann 2005 and Hofmann 2006 report a baseline - anticipatory phase comparison; Al-Shargie 2017, Hafeez 2018 and Ehrhardt 2021 report a control condition - reactive phase comparison; Betti 2017 and Guo 2019 report a baseline - recovery phase comparison.

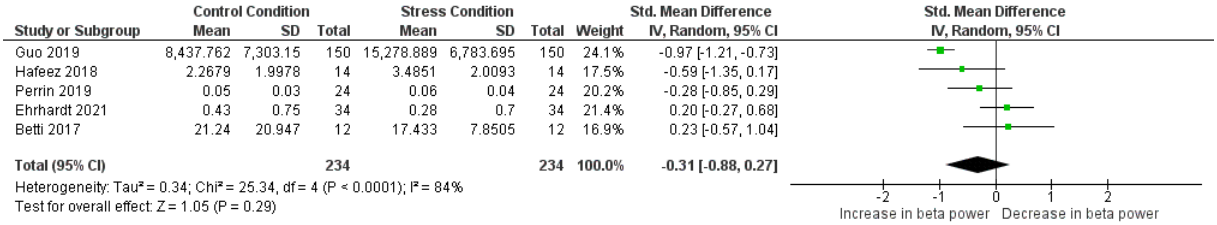

Figure 5. Forest plot illustrating the standardized mean differences (SMD), individual effect sizes, overall effect size and heterogeneity statistics for the meta-analysis examining changes in beta power from a control (non-stressed) condition to a stress condition. Hafeez 2018, Perrin 2019 and Ehrhardt 2021 report a control condition - reactive phase comparison; Betti 2017 and Guo 2019 report a baseline - recovery phase comparison.

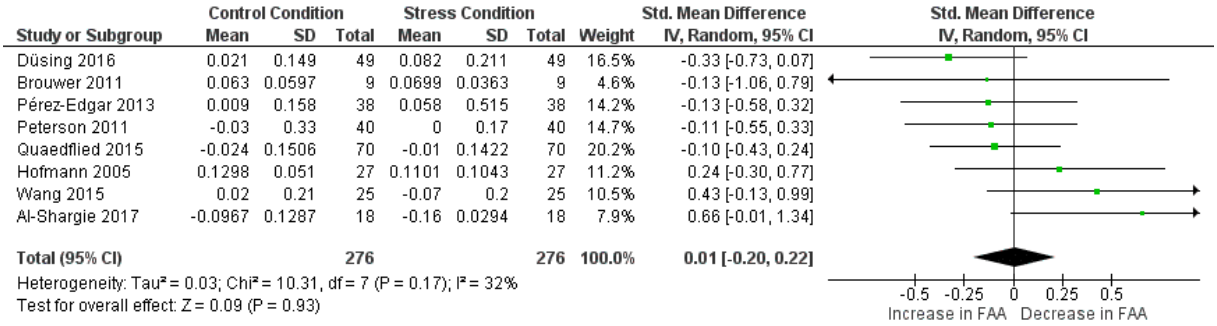

Figure 6. Forest plot illustrating the standardized mean differences (SMD), individual effect sizes, overall effect size and heterogeneity statistics for the meta-analysis examining changes in frontal alpha asymmetry (electrode pair F3-F4) from a control (non-stressed) condition to a stress condition. Hofmann 2005, Pérez-Edgar 2013 and Wang 2015 report a baseline - anticipatory phase comparison; Quaedflied 2015 and Düsing 2016 report a baseline - recovery phase comparison; Brouwer 2011, Peterson 2011 and Al-Shargie 2017 report a control condition - reactive phase comparison.

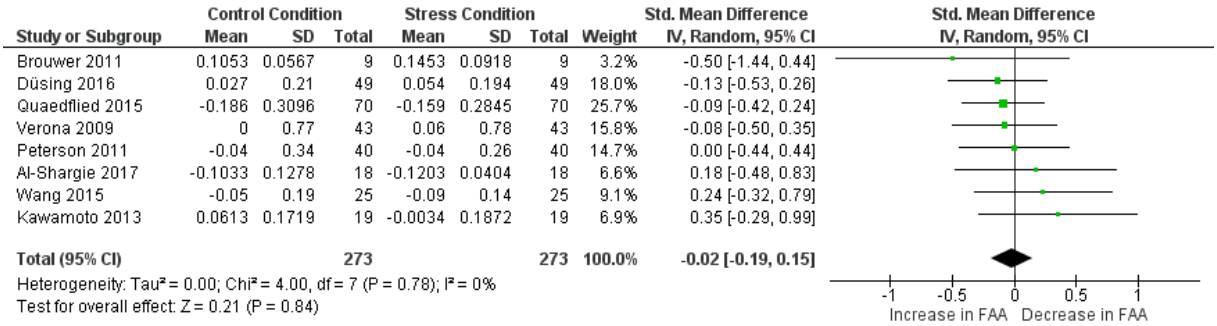

Figure 7. Forest plot illustrating the standardized mean differences (SMD), individual effect sizes, overall effect size and heterogeneity statistics for the meta-analysis examining changes in frontal alpha asymmetry (electrode pair F7-F8) from a control (non-stressed) condition to a stress condition. Wang 2015 report a baseline - anticipatory phase comparison; Quaedflied 2015, Verona 2009 and Düsing 2016 report a baseline - recovery phase comparison; Al-Shargie 2017, Brouwer 2011, Kawamoto 2013 and Peterson 2011 report a control condition - reactive phase comparison.

4. Discussion

In this systematic review and subsequent meta-analyses, we investigated how brain activity of healthy adults, measured by means of EEG spectral analyses, changes due the presence of an acute, laboratory-controlled psychosocial stressor and how these induced changes might vary throughout the three phases (anticipatory, reactive and recovery) of the psychosocial stress response. Results from the systematic review show that a large variety (13 in total) of EEG measures have been employed. Stress phase dependence seems present for some EEG measures, whereas other measures seem more phase independent, show inconsistencies within or between stress phases or are not affected by psychosocial stress. Alpha power shows a relative congruent trend of decreasing under the influence of psychosocial stress, regardless of the stress phase, as ten of the twelve articles investigating alpha power report a significant decrease. This trend is also found in the subsequent meta-analysis of alpha power, since a significant effect size is found (SMD = 0.6, p = 0.001) when evaluating changes in alpha power over all stress phases. Beta power shows a tendency to increase due to psychosocial stress as five out of the eight articles investigating beta power report a significant increase, whereas one article reports an insignificant increase. Two articles report decreases in beta power, although insignificant. However, when investigating changes of beta power over all stress phases through a meta-analysis, no significant effect was found (SMD = − 0.31, p = 0.29). Other measures such as delta power, theta power, relative gamma and theta-alpha power ratio seem to indicate more stress phase dependent changes whereas FAA and coherency do not show consistency between or within stress phases, and the phase-amplitude coupling and amplitude-amplitude correlation do not seem affected by psychosocial stressors. The assessment of stress phase dependence or independence is difficult to assess given that certain stress phases are either overrepresented (reactive phase in alpha power), not investigated (anticipatory phase in beta power), or too little articles have used the specific EEG measure to assess phase dependence systematically. The results will be further discussed by the type of measure (power, power-derived and functional connectivity) which has been investigated. When employing the term “significant” during the discussion, statistical significance ($p < 0.05$) after multiple comparison correction (if applied in the articles) is implied.

Delta power increased during the reactive phase and decreased in the recovery phase (Perrin et al., 2019; van der Veen et al., 2016; Yao et al., 2020). The observed short-term increase in delta power during exposure to a stressor might thus reflect the high salience and motivational relevance of the applied psychosocial stressors within ERP segments (Knyazev,

2012). The observed decrease in delta power after exposure to a psychosocial stressor (i.e., during the recovery phase (Perrin et al., 2019)) might reflect the heightened vigilance of participants. Although the fact that both an increase and decrease in delta power might reflect similar reactions sounds contradictory at first, it should be noted that the articles likely investigate fundamentally different brain mechanisms since van der Veen et al. (2016) as well as Yao et al. (2020) calculate delta power from ERP segments (less than a second long and evoked by a specific stimulus) and therefore investigate stimulus-evoked neural activity whereas Perrin et al. (2019) use longer segments without any stimuli, therefore investigating induced rather than evoked neural activity.

Theta power increased during the reactive phase when analyzing ERP segments from the social judgment paradigm (Somerville et al., 2006). This increase has been found for all ERP segments which contained a psychosocial stressor (Yao et al., 2020), which could, similarly to the increase in delta power, reflect the heightened salience of the stimuli (Knyazev, 2012). Heightened theta power was however also found only in the unexpected rejection condition of the social judgment paradigm (Kortink et al., 2018; van der Veen et al., 2016), which might reflect the involvement of theta oscillations in mechanisms related to both social rejection as well as prediction errors (Hajihosseini and Holroyd, 2013; van der Molen et al., 2017). Contrary to the results from studies investigating evoked neural activity in ERP segments, studies investigating induced neural activity through theta power throughout the reactive phase of the psychosocial stress response report a decrease in theta power compared to a control condition (Hafeez et al., 2018; Minguillon et al., 2016). Research investigating theta power (specifically frontal midline theta) and their relationship with non-psychosocial stressors also reported decreases in theta power, and suggested that difficulties in keeping attention under a stressful condition might be the cause of this decrease (Gartner et al., 2014, 2015). This discrepancy of evoked and induced theta power variations within the reactive phase shows that theta power is reflective of multiple processes within the brain and shows that spectral analysis within ERP segments likely reveals fundamentally different aspects of brain functioning compared to spectral analyses over longer time periods. Whereas the difference between evoked and induced neural activity might explain the contradictory findings, differences between the articles such as participant population and employed psychosocial stressor also likely influence the results, so conclusions regarding contradictory findings should be interpreted with caution.

Alpha power shows a relative congruent trend of decreasing due to psychosocial stress throughout all stress phases. From the twelve articles reporting alpha power results from the various phases of the stress response, ten found significant decreases in alpha power (Al-Shargie et al., 2016, 2017a, 2017b, 2018; Guo et al., 2019; Hafeez et al., 2018; Hofmann, 2006; Hofmann et al., 2005; Minguillon et al., 2016; Yao et al., 2020). This congruency is confirmed by the meta-analysis which shows that the alpha power does, regardless of the stress phase, decrease significantly. The found effect size equals 0.6 ($p = 0.001$), indicating a moderate to large effect size and showing that frontal alpha power is influenced by psychosocial stress. A common assumption regarding alpha power, backed by a significant body of research, is that alpha power is inversely proportional to cortical activity as it likely reflects an inhibitory control system of the brain (Allen et al., 2004; Jensen and Mazaheri, 2010; Mathewson et al., 2011). The reduction of alpha power can therefore be explained by the fact that the psychosocial stress response leads to a state of higher arousal and vigilance as well as the activation of the HPA axis (Campbell and Ehlert, 2012; Kudielka et al., 2004), which leads to higher cortical activity so the individual can correctly cope and adapt to the applied stressor. The results and the accompanying meta-analysis provide convincing evidence to conclude that frontal alpha power is significantly impacted (i.e., reduced) by psychosocial stress, although some caution is warranted. In multiple studies (adaptations of) the Montreal Imaging Stress Task (MIST) have been used to induce psychosocial stress (Al-Shargie et al., 2017a, 2017b, 2017b, 2018; Hafeez et al., 2018; Minguillon et al., 2016). The main difference between the control and stress condition in this paradigm is the presence of a psychosocial stressor (presented by a false comparison to peers as well as the threat from the researchers that if participants do not perform adequately their data is not useable), but time pressure is also added. Ehrhardt et al. (2021) untangled this co-occurrence by letting participants perform a task (the PASAT, Gronwall and Sampson, 1974) with time pressure and with pressure combined with a psychosocial stressor. A drop in alpha power was found in the time pressure + psychosocial stressor condition compared to the time pressure condition, although this drop was not significant. This might indicate that time pressure could be the main driver of alpha power reduction instead of psychosocial stress. Nevertheless, the current meta-analysis only contained two articles employing the MIST (Al-Shargie et al., 2017b; Hafeez et al., 2018), and if these results are removed the effect is still significant (SMD = 0.42; [− 0.06 0.79]. $Z = 2.25$; $p = 0.02$; see supplementary materials for the additional analysis (section 7.6.7.), robustly showing that frontal alpha power is reduced by psychosocial stress.

Sigma power, investigated by a single article (Perrin et al., 2019), did not change in the recovery phase of the psychosocial stress response. This frequency band (13–15 Hz), can be interpreted as a low beta frequency band and is mostly investigated during sleep (D'Rozario et al., 2013). Since sigma power was calculated when participants were awake, the absence of a difference in the recovery phase might be explained by the fact that neural processes in this frequency band are more involved when individuals are sleeping.

Beta power shows a tendency to increase due to psychosocial stress in the reactive and recovery phase. Of the eight articles reporting beta power changes, six report an increase during both phases of the stress response and five articles report a significant increase (Al-Shargie et al., 2016; Guo et al., 2019; Hafeez et al., 2018; Izhar et al., 2019; Minguillon et al., 2016; Perrin et al., 2019). However, both Betti et al. (2018) and Ehrhardt et al. (2021) report a decrease in beta power in response to a psychosocial stressor, although insignificantly. The corresponding meta-analysis shows that overall, no significant effect regarding beta power is found in the reactive and recovery phase (SMD = − 0,34; p = 0, 19). The lack of a significant effect found in the meta-analysis should however be interpreted with caution. Betti et al. (2018) split the beta band in low (13–17 Hz) and high (18–30 Hz) and found that low beta power did increase significantly. Due to the rules applied for the pooling of the data (see supplementary materials for more information; section 7.6.4.), both beta bands were combined, resulting in a decrease in beta power due to the larger range and therefore higher weight of the high beta band. Ehrhardt and colleagues (2021) show, similarly to their results regarding alpha power, that when the psychosocial stressor is split in a time pressure and a social component, no significant difference is found. When both results, however, are compared to a baseline recording a significant increase is reported, again hinting at the fact that beta power increases due to psychosocial stress. Finally, it should be noted that the three articles excluded from the meta-analysis (due to the absence of data or figures or due to a comparison between a resting-state recording and an EEG recording during task engagement) all reported an increase in beta power and thus, although the reasons for exclusion are correct, reaffirm the overall tendency of beta power to increase due to psychosocial stress. The trend of increasing beta power due to psychosocial stress conforms to previous research regarding beta power and stress (Lewis et al., 2007; Tran et al., 2007). Activity in the beta band is assumed to be indicative of cognitive processing (Engel and Fries, 2010; Miller, 2007; von Stein and Sarnthein, 2000), so higher beta power throughout the stress response could be understood as more ongoing cognitive processing. This is likely explained by the fact that neuronal circuits are recruited under the influence of stress, so the

individual is capable of coping and adapting to the demands of psychosocial stressors (De Kloet et al., 2005; Liston et al., 2009; McEwen, 2007). However, the absence of articles investigating beta power in the anticipatory phase and the overall insignificant effect size found in the meta-analysis indicate that more research is needed to validate the identified trend of increases in beta power and to answer the possible stress phase dependence of beta power.

Aside from power measures, another frequently used EEG measure type was power-derived measures. These measures investigate power changes similarly to power measures but combine multiple power values from spatial distinct locations (e.g., FAA, alpha-theta power ratio) or from different frequency ranges (e.g., RG). The most employed power-derived EEG measure is FAA. FAA is an extensively researched measure in psychology and psychiatry research and has been linked to a multitude of psychological constructs and psychiatric disorders (Smith et al., 2017). The recent article by Ocklenburg et al. (2016) has shown the importance of hemispheric laterality, for which FAA can be seen as index, as well as how both chronic and acute stressors can influence this laterality. Building upon the foundation of this article, Berretz et al. (2020) have further expended these principles to neurodevelopmental and psychiatric disorders and show how hemispheric laterality is altered in these clinical populations and how stress can influence this laterality, further showing the importance of FAA as a possible index of psychosocial stress. Thirteen included articles employed FAA and investigated it with respect to psychosocial stress (Al-Shargie et al., 2018; Brouwer et al., 2011; Crost et al., 2008; Düsing et al., 2016; Hofmann et al., 2005; Kawamoto et al., 2013; Minguillon et al., 2016; Papousek et al., 2019; Pérez-Edgar et al., 2013; Peterson et al., 2011; Quaedflieg et al., 2015; Verona et al., 2009; Wang et al., 2015). The meta-analyses for FAA show that, across the three phases, FAA does not change consistently due to psychosocial stress regardless of the electrode pair (for electrode pair F3/F4: SMD = − 0,01; p = 0.93; for F7/F8: SMD = − 0,02; p = 0.84). These results are in line with another meta-analysis regarding FAA as a biomarker for major depressive disorder, as no overall effect was also found (van der Vinne et al., 2017). This lack of overall effect on a group level might be explained by the fact that the relative difference between alpha power of the left and right hemisphere is highly dependent on individual characteristics. FAA is considered as an electrophysiological correlate of approach motivation, which could further explain the high interindividual variability (Smith et al., 2017). The individual variation in FAA is acknowledged by multiple included articles, as their research questions are often aimed at exploring which characteristics are influential for FAA changes. Factors investigated were anger and control (Peterson et al., 2011), defensiveness and anxiety

(Crost et al., 2008), action orientation (Düsing et al., 2016), social anxiety (Hofmann et al., 2005), trait positive affect (Papousek et al., 2019), individual peak alpha frequency (Quaedflieg et al., 2015), time period within a stress phase (Kawamoto et al., 2013) and the change in activation (Pérez-Edgar et al., 2013). It is noticeable that the subdivisions investigated often result in significant differences in FAA, whereas overall no significant effect is found for the investigation of psychosocial stress. Interestingly, only three articles investigated the influence of gender (Pérez-Edgar et al., 2013; Quaedflieg et al., 2015; Verona et al., 2009) and no effect of gender was found in these articles. Another reason for the variable results might be the differences between the cognitive processes which are active when FAA is assessed. The right-shift model, defined by Ocklenburg et al. (2016), proposes that stress often results in an increased activation of mostly the right hemisphere. Changes in FAA are therefore not only dependable on the presence of a psychosocial stressor, but also on the cognitive functions which are active at the same time. If these functions are more left-lateralized, FAA would decrease due to the increased right hemispheric activity induced by a psychosocial stressor. When the active cognitive functions are, however, more right-lateralized, FAA would increase (Ocklenburg et al., 2016). The differences between the stress phases within a single study as well as the differences between studies regarding employed psychosocial stressor likely results in various cognitive functions that are active at different times throughout the stress response, possibly explaining the absence of a uniform change in FAA due to psychosocial stress. Asymmetric brain activity can be assessed from multiple locations. Aside from frontal alpha asymmetry, parietal alpha asymmetry has also been investigated by three articles (Crost et al., 2008; Hofmann et al., 2005; Pérez-Edgar et al., 2013). However, no significant change has been found in this measure. A possible reason for this might be that FAA assesses activity from mainly the (pre)frontal cortex, which is known to contain brain regions involved in higher order cognitive functioning. Given the importance of brain activity reflecting cognitive functioning by the right-shift model of Ocklenburg et al. (2016), it might be possible that the absence of significant changes in parietal alpha asymmetry can be explained by the fact that the parietal regions of the brain are less involved in cognitive processes and asymmetric activity alterations are therefore not found due to the presence of a psychosocial stressor. While no significant changes were reported for parietal alpha asymmetry, it should be noted that parietal alpha asymmetry changes have been observed in patients with major depressive disorder, a stress-related disorder (Jaworska et al., 2012). An absence of significant changes could therefore also be due to methodological aspects such as the employed psychosocial stressor or investigated stressor phase.

Aside from the investigation of hemispheric laterality, another recurring principle of brain activity, the differing functional role of low and high frequency oscillations, is employed in several EEG indices. Low frequency (delta and theta) EEG oscillations seem more prominent during brain states requiring little vigilance or attention, such as drowsiness or sleep (Santamaria and Chiappa, 1987; Susmakov ´ a, ´ 2005). Contrary to this, high frequency EEG (alpha, beta, and gamma) oscillations seem to be more commonly associated with brain states requiring attention and alertness. Alpha oscillations are believed to reflect top-down inhibitory control processes (Jensen and Mazaheri, 2010; Klimesch et al., 2007), beta oscillations have been linked to both emotional and cognitive tasks (Ray and Cole, 1985), and gamma oscillations are also linked to cognitive as well as learning processes (Fitzgibbon et al., 2004; Miltner et al., 1999). When comparing activity from the low frequency ranges to the high frequency ranges, indices reflecting these differences can be constructed. One such index is the slowing ratio, initially defined as an index of cortical arousal in the context of sleepiness of individuals, which is obtained by dividing the power of the lower frequency ranges by the power of the higher frequency ranges (D'Rozario et al., 2013). Perrin et al. (2019) report a decrease in the slowing ratio during the recovery phase (compared to the recovery of a non-psychosocial stressor). This decrease reflects a relative increase of activity in the higher frequency ranges compared to the lower frequency ranges, which possibly shows this heightened state of cortical activity and alertness after psychosocial stress exposure. Another such index is theta-alpha power ratio, which compares theta power (measured at Fz) to alpha power (measured at Pz). The theta-alpha power ratio is reported as indicative of the mental load put on an individual whereby an increase in the ratio corresponds to an increase in mental load (Holm et al., 2009). Under this assumption, an increase in the theta-alpha power ratio during the reactive phase under stressful conditions compared to a control condition, as reported by Subhani et al. (2013), and the disappearance of this difference during the recovery phase, is logical as stress increases the mental load experienced by people, which disappears when the stressor itself is no longer present. The disappearance of the difference during the recovery phase also hints at stress phase dependence, but since only a single article reports results from this measure, no concrete conclusions can be formed. A third index investigating the low-high frequency range differences is relative gamma, which was initially identified in studies investigating effect of meditation on neural activity (Lutz. Et al, 2004; Steinhubl et al., 2015). Here, gamma power is compared to the combined power in the theta and alpha frequency bands. Results from the reactive phase report higher relative gamma values compared to a control condition and a decrease during the recovery phase compared to the reactive phase (Minguillon et al., 2016, 2017; Vaquero-Blasco et al.,

2020, 2021). These results seem mostly driven by changes in the theta and alpha band rather than the gamma band, and high variability exists between participants, showing that psychosocial stress exposure leads to different neurological adjustments between people. Finally, the alpha attenuation coefficient, reflective of sleepiness and drowsiness in participants (Stampi et al., 1995), was decreased during the recovery phase of a psychosocial stressor. This might show that even after the stressor exposure, the brain is still in a state of heightened vigilance, thus possibly showing the long-lasting effects of psychosocial stress on an individual, even when only acute psychosocial stressors are present.

The use of functional connectivity (FC) measures to investigate how the brain adapts to psychosocial stress is less represented in the current literature compared to EEG power (derived) measures, as only four articles have employed such measures (Poppelaars et al., 2018, 2021; Subhani et al., 2016a,b). Poppelaars and colleagues (2018, 2021) employed both phase-amplitude coherence and amplitude-amplitude correlation, FC measures that investigate the interplay between low and high frequency bands. Neither article found significant effects related to the induction of psychosocial stress. The lack of significant effects could have multiple reasons. One possible reason is that the choice of FC measure might be suboptimal for the discovery of brain function alterations related to psychosocial stress. A multitude of FC measures exist, and currently no consensus has yet been reached regarding which FC measure captures the underlying communication between regions best (Bastos and Schoffelen, 2016). Another reason could be that the induction of psychosocial stress was insufficient, but this is not likely as cortisol, considered the gold standard for HPA activation detection, did significantly increase during the paradigm. Subhani et al. (2016a,b) employed coherence and found a multitude of changes due to psychosocial stress. These results should however be interpreted with caution since no multiple comparison correction was employed. Furthermore, the used FC measure (magnitude-squared coherence) overestimates the connections between closely spaced electrodes due to volume conduction, further complicating the interpretation of the results (Nunez et al., 1997).

Overall, the results reviewed in this systematic review and subsequent meta-analyses generally align with the current understanding of the mechanisms of stress. A vast amount of studies investigating psychosocial stress show that, similar to other types of stress, psychosocial stress is taxing on the coping abilities of an individual, therefore requiring additional resources from an individual to correctly cope with the perceived challenges (Berretz et al., 2021; Folkman and Lazarus, 1984; Kogler et al., 2015; McEwen et al., 2015; van Oort et al., 2017).

fMRI research regarding psychosocial stress has shown that during the psychosocial stress response, specific brain regions (the insula, claustrum, and inferior frontal gyrus, for a review and meta-analysis, see Berretz et al., 2021) are more active, likely showing the additional employed resources by the brain. Our results show that, similarly to the results from fMRI studies, increased cortical activity is present during the various phases of the psychosocial stress response. This increased brain activity is mainly found by the fact that alpha power, mainly from the (pre)frontal lobes, decreases consistently throughout the whole stress response, thus indicating the increased activity of the frontal brain regions. Beta power, associated with cognitive processing, shows a trend of increasing throughout the reactive and recovery phase of the stress response, further implicating the increase in brain activity due to psychosocial stress. More complex power and FC measures however are less consistent regarding the psychosocial stress response. This could be because they reflect more specific brain functions and are therefore more subject-specific. The absence of a uniform effect of psychosocial stress on FAA (both in the systematic review as well as in the meta-analyses) could be indicative of this subject-specific brain activity induced by psychosocial stress, as well as the possible different cognitive functions that are active due to the specific circumstances in which psychosocial stress was induced. Although a multitude of results are already present in the current literature, acquiring a general conclusion regarding psychosocial stress and EEG-measured brain activity remains difficult due to methodological and technical reasons. The most notable methodological concern is the large difference in sample sizes (ranging from 6 to 150). The main concern here lies with the articles that use small samples, as this increases the probability of making a type II error. A likely reason for this large variability is the absence of a priori power calculations in all articles, a common occurrence in EEG research (Clayson et al., 2019). This variety however also has implications regarding the meta-analyses conducted in this article, as the overall small number of included articles in the meta-analyses combined with the large variability in sample size limits the certainty of the obtained conclusions. It should be noted, however, that the variability between the included articles of the meta-analyses has been limited as much as possible through the usage of a random effects model and the strict rules regarding phase comparisons that were allowed. Other methodological aspects that further complicate the integration of results are the high variety of employed EEG measures, psychosocial stressor paradigms, and research questions. Variability introduced through the different stressor paradigms is partly reduced since, aside from the articles by Crost et al. (2008) and Verona et al. (2009), all articles employed a within-subjects design, therefore avoiding possible differences between the compared groups when comparing a stress phase to its non-

stressed counterpart. It is still possible however that changes in the EEG measures are partially due to differences between the obtained baseline recordings or control conditions. Differences due to the employed stress paradigm are most likely present in the reactive phase, since during this phase participants are engaged with a task and task-specific neural activity is likely present in the EEG signal. The high diversity of research questions also explains part of the low scores regarding the risk of bias analysis since this discrepancy leads to the absence of information necessary for our research questions.

From a technical point of view, some aspects should also be considered when interpreting the results. Variations in the selected electrodes, preprocessing and analysis steps as well as the definitions of the used frequency bands between the articles could introduce small differences in the reported findings (Gutmann et al., 2018; Robbins et al., 2020). Another technical aspect that should be considered is the influence of volume conduction. Volume conduction, understood as the propagation of electrical fields through biological tissue, results in the recording of electrical activity from a single source within the brain by multiple electrodes across the scalp. For the results of FAA, and specifically FAA calculated from the F3/F4 electrode pair (as these electrodes lie closely together), volume conduction probably has an influence. It is likely that both electrodes recorded alpha activity from similar sources, further complicating the results. When evaluating the results of other EEG measures that employ location-specific electrodes for their calculation, such as coherence and theta-alpha power ratio, the influence of volume conduction should also be considered. Future research should therefore consider additional preprocessing or analysis steps, such as a surface laplacian, to reduce the influence of volume conduction (Kayser and Tenke, 2015). Finally, it should be mentioned that up until now electrical source imaging, referring to the mathematical operations that allow one to calculate the activity of various regions in the brain from surface recordings (Michel and Brunet, 2019), has not yet been employed with regard to psychosocial stress. This technique could be considered in future research to further investigate how psychosocial stress affects the brain.

5. Conclusion

In conclusion, the current literature regarding psychosocial stress and spectral EEG analyses shows that psychosocial stress results in measurable changes in several EEG indices, which exhibit both stressor response phase specific and aspecific tendencies. Alpha power consistently decreases due to acute, laboratory psychosocial stressors, regardless of the stressor phase. Beta power shows a tendency of increasing during the reactive and recovery phase, but this tendency should be interpreted with caution since no significant effect was found in the subsequent meta-analysis. The results from other EEG measures, such as delta power, theta power, relative gamma and theta-alpha power ratio, imply that these measures show stress phase dependence. Other measures, such as FAA and coherence show variable results regarding their stress phase dependency. Although significant work has already been performed which shows the importance of stress response phase when investigating EEG measures, the high variability in both methodological as well as technical aspects complicates the integration of the results towards an overall conclusion regarding psychosocial stressors and EEG-measured brain activity. Therefore, future work is needed to clear up how the stressor phases, stress paradigms and analysis steps have an influence on neural activity and their corresponding spectral EEG measures.

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7. Supplemental information

7.1. Alterations from the published article

The final text above has some slight alterations from the published article in *Neurobiology of Stress*. None of the alterations are related to the substance, but are done for the presentation of the article in its current form. These alterations are:

- Figure 1 : font change and enlargment of words.
- Figure 2 : font change and enlargment of words.
- Figure 3 : font change, enlargments of words, and minor adjusments to the placement.
- Table 1 : font change, merge of columns (Author & Year; Participants & Participants (male)), change of the representation of the *Participants (male)* column information, change of the representation of the *Age (M, STD)* column information, change of the words ‘delta’, ‘alpha’, ‘sigma’, ‘beta’, ‘gamma’ to the corresponding greek letters in the *FR (Hz)* column.
- Text : throughout the text supplementary materials are mentioned. Initially the full name of the material was given, but this is changed to the specific sections found in this document. The names of the sections are identical to those mentioned in the published article.

7.2. Acknowledgments

We thank the reviewers for their constructive comments as the final article was significantly improved due to their feedback.

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7.4. Declaration of competing interest

All authors report no financial interests or potential conflicts of interest related to this publication.

7.5. Open practices statement

Supplementary data can be found online at: https://doi. org/10.1016/j.ynstr.2022.100452.

7.6. Supplementary materials

7.6.1. Risk of bias analysis – explanation of scoring

For this review, the questions were adjusted from the *Standard Quality Assessment Criteria for evaluating primary research papers from a variety of fields* (Kmet et al., 2004) to capture the specific technical aspects of EEG measurement and analysis.

Question 8 ("Outcome and (if applicable) exposure measure(s) are well defined and robust to measurement/misclassification bias? Means of assessment reported?") has been split up into two sub questions (8a: Outcome measure (EEG measure); 8b: exposure measure (stressor))

Question 10 ("Analytic methods described/justified and appropriate?") has been split up into three sub questions (10a: EEG equipment information; 10b: preprocessing information; 10c: statistical analysis).

The final score for question 8 and 10 is calculated by employing the following rule: if all sub questions are reported completely the overall score is yes, if no sub question is answered the overall score is no and otherwise the overall score is partial.

Q1: Question/objective sufficiently described?

- Yes: study objective and research question(s) are sufficiently described
- Partial: stuby objective and research question(s) is mentioned, but is not completely clear or needs to be assessed from parts of the article other than the abstract or introduction
- No: study objective and research question(s) are not clearly described

Q2: Study design evident and appropriate?

- Yes: study design is appropriate for investigation of EEG changes due to psychosocial stress
- Partial: Due to the study goal, which does not always allign with the interest of this systematic review, the study design is not completely appropriate.
- No: Study design is not appropriate.

Q3: Method of subject/comparison group selection or source of information/input variables described and appropriate?

- Yes: both the recruiting method as well as the reimbursement (if any) is given
- Partial: one of both is given
- Nothing is given

Q4: Subject (and comparison group, if applicable) characteristics sufficiently described?

- Yes: Both male-female amount and mean + std age is given
- Partial: one of the two is given
- No: neither is given

Q5: If interventional and random allocation was possible, was it described?

- Yes: randomization is mentioned and explained
- Partial: randomization is mentioned, but not explained
- No: not mentioned, not explained
- N/A: the study is a within-subjects design (this equals to a "Yes" (= 2))

Q6: If interventional and blinding of investigators was possible, was it reported?

- N/A: Since the goal of the studies is the induction of psychosocial stress, the investigators will always be aware of the paradigm and can therefore not be blinded. Therefore a score of "Yes" (=2) is always given

Q7: If interventional and blinding of subjects was possible, was it reported?

- Yes: A cover story is mentioned and the content of the cover story is given
- Partial: A cover story is mentioned, but not explained OR the cover story is interwoven in the paradigm (MIST, TSST,…)
- No: No cover story is mentioned

Q8: Outcome and (if applicable) exposure measure(s) well defined and robust to measurement/misclassification bias? Means of assessment reported?

Q8a: Outcome measure

- Yes: the EEG measure and its calculation is described fully
- Partial: the EEG measure is mentioned, but it is not described how it is calculated
- No: EEG measure is not described

Q8b: Exposure measure

- Yes: the stressor is described fully
- Partial: the stressor is described, but not fully (no timing considerations etc.)
- No: the stressor is not descrbied

Q9: Sample size appropriate?

- It is assumed that the investigation of stress can be approached as looking at the difference between two measurement times. Therefore a sample size of 50 is considered to be large enough to correctly investigate this research question. Sample sizes of 30+ will be considered as partially adequate.

Q10: Analytic methods described/justified and appropriate?

Q10a: EEG equipment information

- Yes: all important EEG equipment and recording information is described (channel amount, placement, impedance, sampling rate, reference)
- Partial: some variables are described
- No: no variables are described

Q10b: Preprocessing

- Yes: all important preprocessing steps are described (Filtering (LP, HP, Bandstop), rereferencing, artifact removal, epoch length)
- Partial: some variables are described
- No: no variables are described

Q10c: Statistical analysis

- Yes: statistical analysis is fully described (test statistic, test value, p value, multiple testing correction, effect size)
- Partial: statistical analysis is described, but not all important variables are given
- No: no statistics are described

Q11: Some estimate of variance is reported for the main results?

- Yes: Mean values with SEM or STDs are given
- Partial: Mean values with SEM or STDs are shown in figures
- No: No mention of SEM or STDs

Q12: Controlled for confounding?

- Yes: Considerable effort has been put into the elimination of possible confounders (handedness, cicardian rythm, male-female composition, neurological/psychiatric disorder presence, medication intake, exercice food intake hours before the experiment,…)
- Partial: Some effort has been put into confounding elimination, but important aspects are missing.
- No: Little to no effort has been put in confounder elimination

Q13: Results reported in sufficient detail?

- Yes: All mentioned measurements and outcomes are presented and explained in sufficient detail
- Partial: Quantitative results are explained for most outcomes, but some are missing or it is not clear which measures will be investigated specifically and no predictions are present
- No: One or several Outcomes are missing, no explanation of which outcomes will be investigated

Q14: Conclusions supported by the results?

- Yes: all conclusions are supported by the results
- Partial: Some conclusions are supported by the results, but some are not (eg. negative results are ignored etc.) OR no mention of the small sample size regarding the results is discussed
- No: Conclusions are not supported by the results

7.6.2. Risk of bias analysis – extended calculation

This supplemental material is an excel file with multiple headings, so it is not presented here. It can be found following the link provided in section 7.5.

7.6.3. Systematic review – extracted information

This supplemental material is an excel file with multiple headings, so it is not presented here. It can be found following the link provided in section 7.5.

7.6.4. Meta-Analysis – data extraction procedure

Given the length of this supplemental material, and the fact that pictures from the included articles are present, it is not presented here. It can be found following the link provided in section 7.5.

7.6.5. Meta-Analysis – numbers

This supplemental material is an excel file with multiple headings, so it is not presented here. It can be found following the link provided in section 7.5.

7.6.6. Meta-Analysis – publication bias analysis

Funnel plots and Egger's test results (Egger et al., 1997) have been obtained using the R software language. The following R packages have been used to obtain the results: *meta*, *dmetar*. The code for each publication bias analysis can be found on the following GitHub page: https://github.com/dx2r/Systematic-Review-and-Meta-Analysis-Psychosocial-stress-EEG-.git It should be noted that the Egger's test might not have sufficient power to detect publication bias due to the relative small amount of studies in each meta-analysis (Sterne et al., 2011).

Reference for the Egger's test:

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj*, 315(7109), 629-634.

Reference for the Egger's test power:

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., ... & Higgins, J. P. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj*, 343.

7.6.6.1. Alpha power meta-analysis

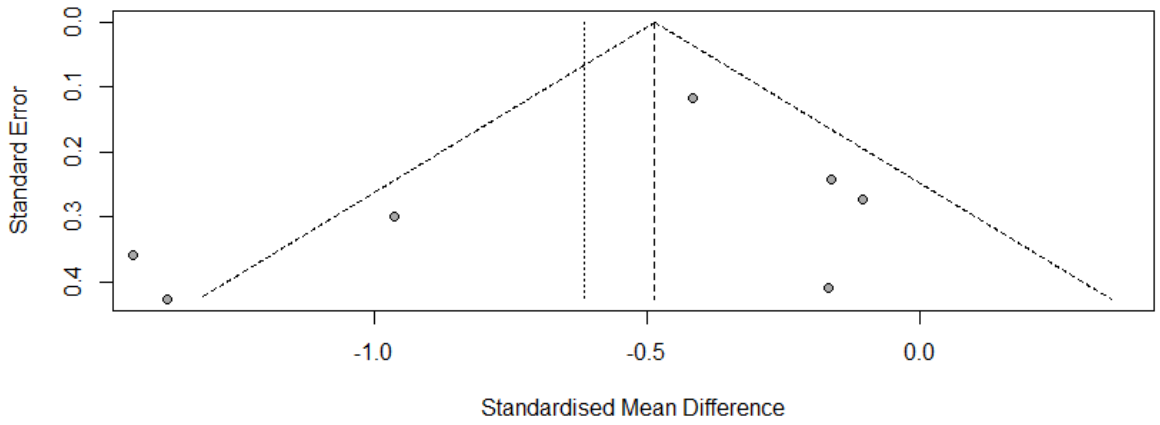

Figure (extra): Funnel plot of the alpha power meta-analysis results.

Corresponding Egger's test results:

Intercept: -1.53841

Lower bound (95% confidence): -4.373

Upper bound (95% cconfidence): 1.296

t-value: -1.0639

p-value: 0.336

Conclusion:

The results of the Egger's test show no indication of a publication bias. In addition, no apparent funnel plot asymmetry is present.

7.6.6.2. Beta power meta-analysis

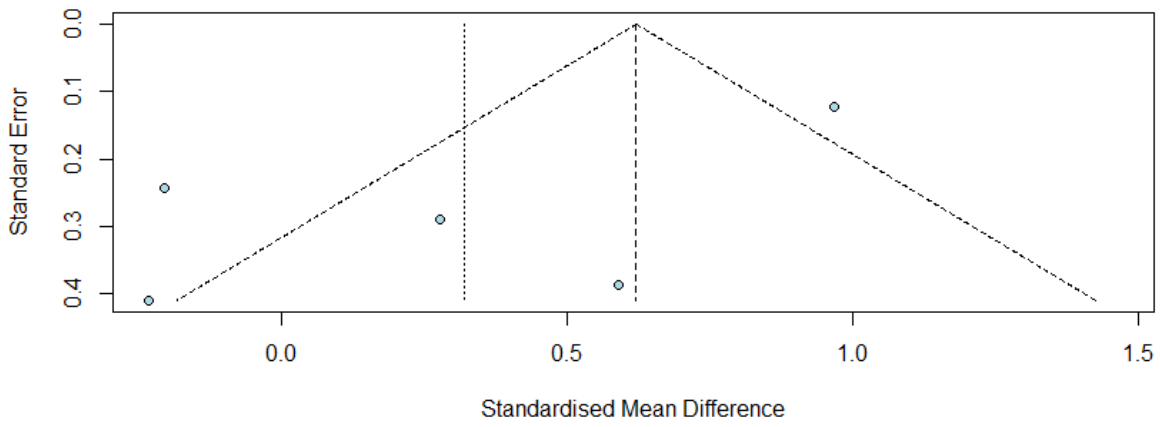

Figure (extra): Funnel plot of the beta power meta-analysis results.

Corresponding Egger's test results:

Intercept: -3.801

Lower bound (95% confidence): -7.44

Upper bound (95% cconfidence): -0.17

t-value: -2.049

p-value: 0.13

Conclusion:

The results of the Egger's test indicate that no significant publication bias is present. However, the funnel plot shows that four articles lie on the left side of the plot, indicating funnel plot asymmetry. Therefore, it can be concluded that some publication bias is present for the beta power analysis.

7.6.6.3. Frontal alpha asymmetry (F3-F4) meta-analysis

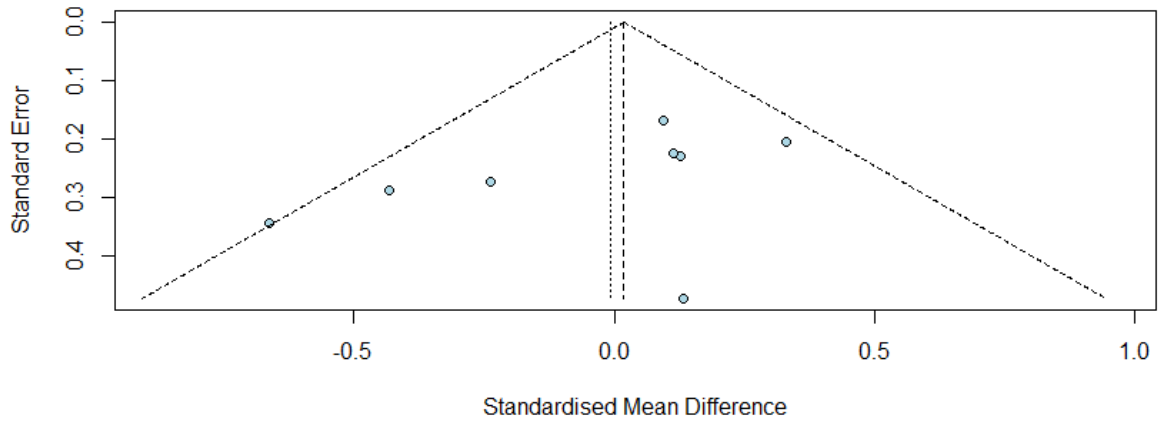

Figure (extra): Funnel plot of the frontal alpha asymmetry (F3-F4) meta-analysis results.

Corresponding Egger's test results:

Intercept: -2.345

Lower bound (95% confidence): -5.14

Upper bound (95% cconfidence): -0.45

t-value: -1.642

p-value: 0.15

Conclusion:

The results of the Egger's test show no indication of a publication bias. In addition, no apparent funnel plot asymmetry is present.

7.6.6.4. Frontal alpha asymmetry (F7-F8) meta-analysis

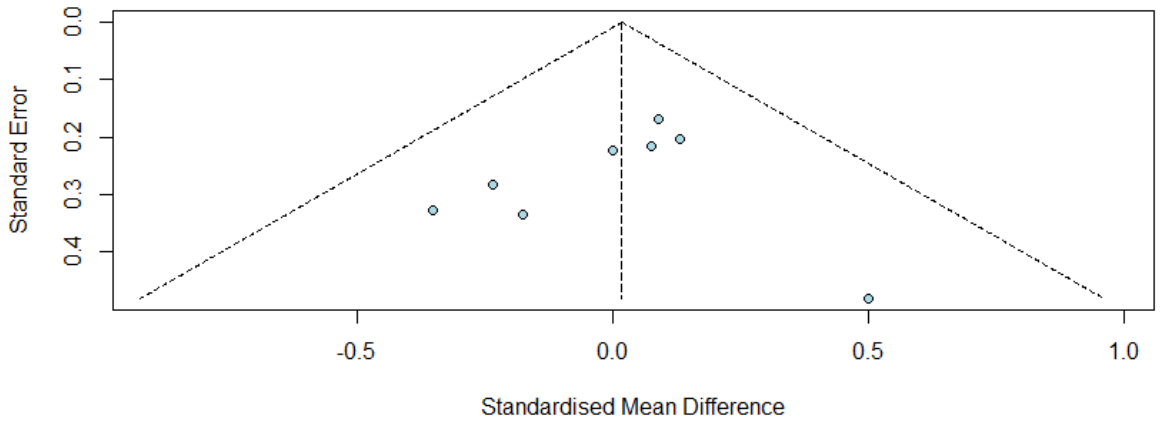

Figure (extra): Funnel plot of the frontal alpha asymmetry (F7-F8) meta-analysis results.

Corresponding Egger's test results:

Intercept: -0.637

Lower bound (95% confidence): -2.56

Upper bound (95% cconfidence): -1.29

t-value: -0.649

p-value: 0.54

Conclusion:

The results of the Egger's test show no indication of a publication bias. In addition, no apparent funnel plot asymmetry is present.

7.6.7. Meta-Analysis – additional calculation

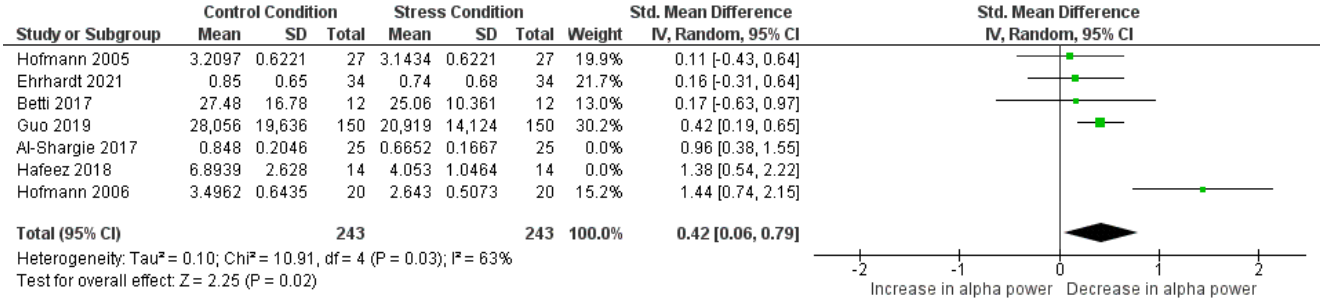

Figure (Extra): Forest plot illustrating the standardized mean differences (SMD), individual effect sizes, overall effect size, and heterogeneity statistics for the meta-analysis examining changes in alpha power from a control (non-stressed) condition to a stress condition, without the articles that employ the Montreal Imaging Stress Task (MIST). Hofmann 2005 and Hofmann 2006 report a baseline - anticipatory phase comparison; Al-Shargie 2017, Hafeez 2018 and Ehrhardt 2021 report a control condition - reactive phase comparison; Betti 2017 and Guo 2019 report a baseline - recovery phase comparison.

Chapter 3

Uncovering the underlying factors of ERP changes in the Cyberball paradigm: a systematic review investigating the impact of ostracism and paradigm characteristics

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Abstract

The Cyberball is the most commonly employed paradigm for the investigation of the effects of social exclusion, also called ostracism. The analysis of event-related potentials (ERPs), short-term stimulus-induced fluctuations in the EEG signal, has been employed for the identification of time-sensitive neural responses to ostracism-related information. Changes in ERPs during the Cyberball are normally attributed to the effect of ostracism, but it has been argued that characteristics of the paradigm, not ostracism, are the driving force for these changes. To elucidate the origin of the ERP changes in the Cyberball, we systematically reviewed the Cyberball-ERP literature of healthy, adult populations, and evaluated whether the social context of ostracism or characteristics of the paradigm are better suited for the explanation of the found results. Our results show that for many components no clear origin can be identified, but that expectancy violations, not ostracism, best explains the results of the P3 complex. Future research should therefore also employ other paradigms for the research into the effects of ostracism on ERPs.

1. Introduction

Humans are a social species and rely heavily on other individuals for survival throughout their lives (R. F. Baumeister & Leary, 1995). Sufficient and positive social interactions with others are vital for both physical and mental well-being of the individual (Holt-Lunstad, 2018; Ono et al., 2011). The presence of positive social environments throughout life has therefore consistently been associated with improved physical and mental health while their absence, or the presence of aversive environments, has been linked with health complications (J. T. Cacioppo & Cacioppo, 2014; Orben et al., 2020; Umberson et al., 2010). Social interactions are highly complex and can be threatened in a variety of ways. One such potent threat is social exclusion, commonly called *ostracism* (R. F. Baumeister et al., 2007). Ostracism is experienced as stressful and painful, and results in feelings of loneliness, which is known to be harmful to mental and physical health (Beekman et al., 2016; J. T. Cacioppo & Cacioppo, 2014; Eisenberger et al., 2003; Eisenberger, 2012). Loneliness has consequently been linked with a great amount of physical and mental problems such as increased blood pressure (J. T. Cacioppo et al., 2002; Hawkley et al., 2006, 2010), sleep deprivation and fragmentation (Griffin et al., 2020; Kurina et al., 2011), dementia (Holwerda et al., 2014; Sutin et al., 2020), depression (Beutel et al., 2017; J. T. Cacioppo et al., 2010), anxiety (Beutel et al., 2017), suicide (Stravynski & Boyer, 2001), and general increased mortality risk (Luo et al., 2012; Rico-Uribe et al., 2018).

Aside from the investigation of the consequences of ostracism, significant efforts have been made towards delineating the concept itself. An early conceptualization of how individuals experience ostracism is the *sociometer model*, proposed by Leary and colleagues (1995), which describes self-esteem as an internal "gauge" for an individual's social status that, when detecting exclusionary threats, results in adaptive behavior aimed at maintaining and re-establishing the threatened social connections (Leary et al., 1995). A model of social ostracism itself, the *need-threat model*, was proposed two years later by Kipling D. Williams (1997), who defines a taxonomic structure based on visibility, motive, quantity, and causal certainty, evaluates antecedents (i.e., individual differences; social/situational forces), mediators (i.e., the attribution for ostracism; individual differences), and reactions (both short- and long term). Williams (1997) further specified four fundamental needs: belonging, self-esteem, control, and meaningful existence, that are prevented from being fulfilled when experiencing ostracism and can be measured with the *need-threat questionnaire* (NTQ). Aside from the need-threat model, Williams also proposed a "ball-tossing" paradigm for the investigation of ostracism. In this paradigm, a participant is seated in a room with two confederates who in reality are accomplices

of the experimenter and aware of the experiment. One of the confederates starts throwing a ball around and initially, the participant is included in the game but after a short time (around one minute) the confederates only throw the ball to each other and ignore the participant until the end of the experiment (Williams, 1997). This paradigm was later transformed into a computer task where, rather than being excluded in real life, participants were excluded virtually on a computer screen, called the Cyberball (Williams et al., 2000). Throughout the following decades the Cyberball has, likely due to its simple interface and reliable ostracizing effects, grown into the central experimental paradigm used for the investigation of (social) ostracism.

In its most basic form, the Cyberball consists of two conditions, an *inclusion condition*, where the participant receives the ball as much as the confederates (i.e., 33% of all throws, when two confederates are present), and an *exclusion condition*, where the participant either receives the ball less often (i.e., *partial* ostracism, 16-20% of all throws; Williams et al., 2000) or not at all (i.e., *total* ostracism, 0% of all throws; Williams et al., 2000). As the supposed confederates are computer-generated personas, the amount of throws towards the participant in each condition is predetermined while the participant believes they are playing with actual humans. This consequently results in strong feelings of ostracism during the exclusion condition (Hartgerink et al., 2015). Aside from the in- and (both partial and complete) exclusion conditions, Williams and colleagues (2000) further defined an *overinclusion* condition, where participants received the ball more often than normal. This condition was included to make participants self-aware and conspicuous without being excluded from the game and has been employed to question whether individuals only react to exclusionary information (conform to the sociometer hypothesis) or if social information is processed as a continuum ranging from overinclusion to complete ostracism (Niedeggen et al., 2014). Additional conditions have been added to the initial paradigm by other researchers, such as the *control condition* (i.e., the participant watches the Cyberball without participating and thus does not feel excluded; Eisenberger et al., 2003), and the *re-inclusion condition* (i.e., after the exclusion condition, the participant is included again; Themanson et al., 2013). Aside from the conditions, three different throw types can also be defined within each condition. Firstly, the participant can throw the ball to either confederate (*eject* throws), secondly, one of the confederates can throw the ball to the participant (*receive* throws), and finally a confederate can throw the ball to the other confederate (*neglect* throws). The Cyberball paradigm and the different throw types are shown in Figure 1. Whereas most studies investigate the differences between the conditions of the paradigm

(i.e., inclusion and exclusion), differences between the throw types (i.e., receive and neglect) have also been studied.

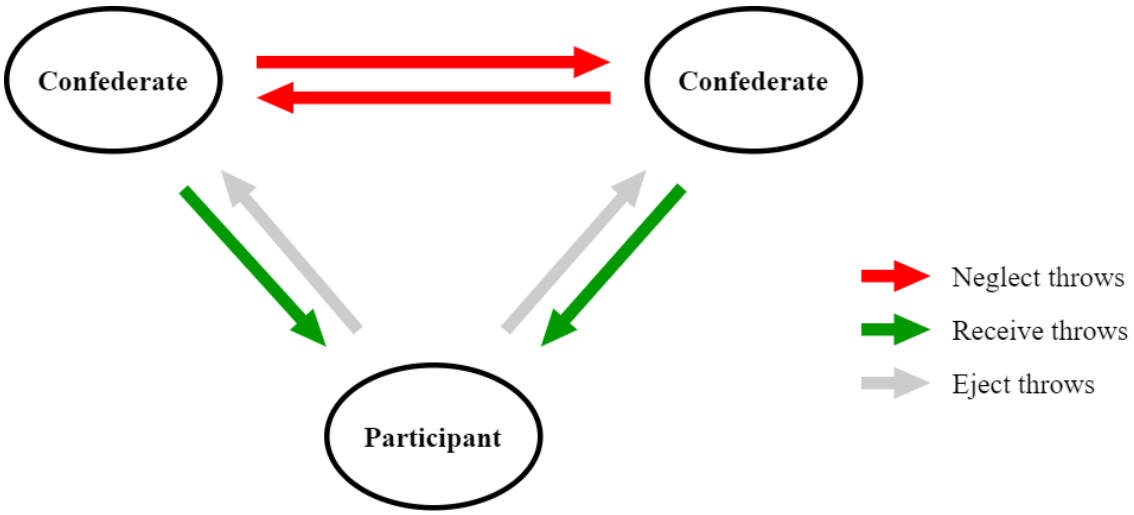

Figure 1: Illustration of the different throw types in the Cyberball paradigm.

Another important reason for the popularity of the Cyberball is the fact that it can easily be conducted within the limitations imposed by neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), which makes it possible to investigate the neural processes related to ostracism. Given the primordial importance of healthy social bonds, it is reasonable to assume that specialized neural mechanisms have evolved that can interpret and process social stimuli and evoke behavioral adjustments aimed at optimizing future social interactions (Insel & Fernald, 2004; Kerr & Levine, 2008). The Cyberball has consequently been used extensively for the identification of the so-called *neural alarm system*, a circuit in the brain specialized at detecting exclusionary stimuli. The first stage of this neural system is assumed to be automatic, continuous, involuntary, and unconscious (Kerr & Levine, 2008; Leary et al., 1995; Williams, 2007, 2009; Zadro, Williams & Richardson, 2004), and empirical studies have identified the anterior cingulate cortex (ACC) as the main region active during this stage (Eisenberger et al., 2003; Eisenberger & Lieberman, 2004; Mwilambwe-Tshilobo & Spreng, 2021). Given that ACC activation is also observed for other, non-social stimuli, it has been proposed that this activity reflects conflict monitoring, a general function of cognitive control that detects stimuli that conflict with expected or desired outcomes (Botvinick et al., 2001). The increased activity of the ACC during ostracism can thusly be understood as the detection of socially conflicting stimuli, processed in the dorsal subsection of the ACC (Botvinick et al., 2001; Somerville et al.,

2006; van Veen et al., 2001; Eisenberger & Lieberman, 2004). The second stage of the alarm system involves cognitive appraisal and regulatory functions that are directed toward the adjustment of top-down control over the subsequent processing of exclusionary information and has mostly been linked with regions of the prefrontal cortex (Botvinick et al., 2011; Kerns et al., 2004; MacDonald et al., 2000; Themanson et al., 2013; Williams, 2007). Results from systematic reviews and meta-analyses of fMRI studies have identified additional regions, such as the posterior cingulate cortex, the insulae (both anterior and posterior), temporal regions, the cerebellum, the basal ganglia, and the (pre)motor areas, likely involved in the emotional response to ostracism (Berretz et al., 2021; S. Cacioppo et al., 2013; Mwilambwe-Tshilobo & Spreng, 2021; Wang et al., 2017).

Aside from fMRI, EEG has been increasingly used for the investigation of neural activity concerning ostracism. Although spatially inferior to fMRI, EEG has a higher temporal resolution and can thus elucidate temporal dynamics of neural activity that are not captured with fMRI. The analysis of *event-related potentials* (ERPs), small voltage fluctuations in the EEG signal following shortly (order of milliseconds) before or after the presentation of a stimulus reflecting the processing of said stimulus, has become the standard for investigating time-sensitive neural responses in the Cyberball paradigm. Multiple ERP components, specific subsections of the ERP signal identified by their polarity (positive or negative) and latency (Blackwood & Muir, 1990; Ibanez et al., 2012), have been identified in the Cyberball and have subsequently been linked to the aforementioned neural alarm system. The first stage of the neural alarm system has been linked with the N2 component, where a larger N2 component reflects the automatic detection of any exclusionary (i.e., conflicting) stimuli, driven mostly by increased ACC activity (Donkers & Van Boxtel, 2004; Folstein & Van Petten, 2008; Larson et al., 2014; Yeung et al., 2004; Zadro, Williams & Richardson, 2004), while the second, more cognitive stage is believed to be indexed by components of the P3 complex, the P3a and P3b (Folstein & Van Petten, 2008; Polich, 2007), where larger P3a amplitudes reflect the induction of negative mood and P3b, whose amplitude changes are (sometimes) correlated with changes in NTQ subscales, reflects stimulus evaluation and categorization (Gutz et al., 2011, 2015; Kawamoto et al., 2013; Niedeggen et al., 2014, 2017; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015, 2016). Later components such as the late positive potential (LPP) are further assumed to index regulatory emotional responses (Crowley et al., 2009; Kross et al., 2011). Additional components such as the Contingent Negative Variation (CNV) and P2 have also been studied in the last two decades.

Some of these results (combined with results from a multitude of fMRI studies) have been integrated into a theoretical model that possibly explains how the brain reacts to ostracism in the Cyberball paradigm, proposed in a scoping review by Wang and colleagues (2017). In this model, built upon an earlier theoretical model of Kawamoto and colleagues (2015), Wang and colleagues (2017) propose a two-stage neural framework for the explanation of ostracism-related information processing. The *early first stage* (200-300 ms post-stimulus), reflecting the perception, detection, and attention toward ostracism-related information, is identified by two ERPs: the P2 and N2. The included studies show that the amplitude of both the P2, understood to reflect the perception and processing of salient stimuli (Key et al., 2005; Luck & Hillyard, 1994), and the N2, indicative of the activation of a neural alarm activation related to conflict monitoring (Themanson et al., 2013; Weschke & Niedeggen, 2013), is increased during the exclusion, compared to the inclusion condition. The *late first stage* (300-400 ms post-stimulus) is proposed to indicate the induction and subsequent appraisal of the exclusion event. It is characterized by the P3 complex and its subcomponents, the P3a and P3b. Similarly to the first stage, increased amplitudes for both the P3a, related to the negative induced mood (Gutz et al., 2011; Weschke & Niedeggen, 2013), and P3b, reflecting stimulus evaluation and categorization (Gutz et al., 2011; Weschke & Niedeggen, 2013, 2015; Wronka et al., 2012), have been reported. The *second stage* (400-900 ms post-stimulus), identified by an increased LPP is suggested as the period in which emotion regulation of the stimuli occurs (Crowley et al., 2009; Kross et al., 2011).

Although the ERP results in the model of Wang and colleagues (2017) are clear, opinions differ on what they exactly reflect. Given the short timeframes in which ERPs occur and the fact that they are found in a great variety of both social and non-social paradigms, it has been proposed that rather than reflect ostracism-related neural processing, ERP component changes in the Cyberball paradigm instead are induced by other characteristics of the Cyberball that are not related to ostracism. This critique originates from two sources: the adaptations made to the Cyberball paradigm in order to conduct reliable ERP research, and characteristics of the paradigm unrelated to the social context that possibly influence ERP components. Behavioral studies regarding ostracism commonly use a between-subjects design where participants are only exposed to a single condition (Hartgerink et al., 2015), while neuroimaging studies rely on within-subjects designs given that aside from the activity induced by the paradigm, additional neural activity is present, making between-subject designs impractical. While within-subject designs come with increased statistical power (Charness et al., 2012), it introduces

several possible issues. Firstly, within-subjects designs might decrease the believability of the cover story as it is difficult to convince participants that after being included in a first condition, participants are suddenly excluded without a clear reason. The usage of within-subject designs further introduces expectations in the participants as they expect the same setting in the second condition compared to the first. Expectancy violations have known influences on ERP components, especially the P3 complex (Polich, 2008), possibly making it difficult to disentangle the specific contributions of ostracism from the aforementioned violations. Secondly, given the fragility of the cover story, some researchers have consequently adjusted the paradigm by giving participants no self-report questionnaire after the first condition, given that questions related to being excluded might give away the true reason for the experiment, and let participants fill out the questionnaires after the second condition. Although this approach might be beneficial for the believability of the experiment, it possibly decreases the validity of the questionnaires given the time delay between the exposure and self-reports, and the presence of an additional condition in between both events. Aside from this, most ERP studies have employed partial exclusion as this condition still contains receive throws, making it possible to investigate changes regarding this throw type across conditions. While still able to reliably induce feelings of ostracism in participants, the effect is smaller compared to complete exclusion (Williams et al., 2000), which is the most commonly employed condition in behavioral studies (Hartgerink et al., 2015). Further changes to the paradigm are related to the technical aspects of ERP analysis. ERPs have a low signal-to-noise ratio and therefore multiple trials are needed for each specific event to obtain reliable estimates of the ERPs (Luck, 2014). This requirement consequently increases the amount of throws and time that is needed for each condition. Contrary to studies investigating behavioral effects of ostracism where throw amounts rarely exceed 40 and the total duration of the paradigm almost never exceeds five minutes (Hartgerink et al., 2015), Cyberball ERP studies commonly have more than 100 throws and take longer than five minutes to complete a single condition. In their meta-analysis, Hartgerink and colleagues (2015) carefully suggest that increasing throws might lead to a “more diffused” ostracism effect. Considering the much lower throw amount of the included studies, it is reasonable to assume that the throw amounts employed in Cyberball ERP studies might have a significant diminishing effect on the perceived ostracism of the participants, while additionally possibly introducing other neural, psychological, or behavioral effects. Another possible issue is related to how the measures reflecting the ERP components are obtained. Given the low signal-to-noise ratio, EEG trials of the same event are averaged before computing the final value representing the component (Luck, 2014). This averaging however comes with the

implicit assumption that each trial has measured a very similar neural process, but this might be incorrect as different individuals might feel excluded earlier or later throughout the exclusion condition. This issue is most important for ERP components indexing the second stage of the neural alarm system such as the P3a or P3b as these reflect more cognitive processes while the N2 component (assumed to reflect the unconscious detection of exclusionary stimuli) should theoretically not be influenced by this. It should be noted that some studies partly account for this potential issue by omitting a few neglect trials after receiving the ball during the exclusion condition.

Aside from adaptations to the Cyberball for ERP research, characteristics of the paradigm itself might also influence the results. A first characteristic to consider is the fact that the in- and exclusion conditions of the Cyberball paradigm differ, aside from the overarching social context, in the probability of each throw occurrence. While both the receive and neglect throws occur equally in the inclusion condition, neglect throws are more common in the exclusion compared to the inclusion condition. This conditional difference is of significant importance as occurrence probability of stimuli has well-known effects on both P3a and P3b amplitudes (Polich, 2007). These effects are acknowledged by almost all studies investigating the P3 component, and has specifically been investigated by Weschke & Niedeggen (2015, 2016). Focussing on the P3b component, Weschke and colleague concluded that the P3b seems not a part of an "exclusion-specific neural alarm system", but is likely related to expectancy violations (i.e., events with low probability are not expected, so if they occur an update of the mental model of an individual is required; Polich, 2007). A second characteristic to consider is that an action is required when a participant receives the ball, which is not the case if confederates throw the ball to each other. Some articles have consequently argued that neglect throws require response inhibition (Weschke & Niedeggen, 2016). This cognitive process is known to elicit an N2 component (Jodo & Kayama, 1992; Kaiser et al., 2006) and influences the amplitude of the P3 complex (Albert et al., 2013), possibly complicating the interpretation of these components as indices of the neural alarm system.

The debate of what neural processes are measured during the Cyberball paradigm is not unique to the field of ERP research but is also seen in fMRI studies. Wang and colleagues (2017) addressed this debate and concluded that activity of the dorsal anterior cingulate cortex (dACC) is more related to cognitive processes associated with conflict monitoring, emotional awareness, and reward-based decision-making, rather than complementary processes of a neural alarm system. This conclusion is substantiated by the work of Somerville and colleagues

(2006), who found that expectancy violation and social rejection (i.e., a closely related, but distinct social stimulus from ostracism whereby individuals or groups are explicitly declared to be unwanted, contrary to less directly ignoring or excluding individuals, encapsulated by the term ostracism; Williams, 2007) elicit differential activations in the ACC, whereby the dorsal ACC is activated by expectancy violations and the ventral ACC by social exclusion. Although these results highlight that expectancy violation and social rejection is processed separately within the brain, this conclusion can unfortunately not be extended to the field of ERPs. Given the lower temporal resolution of fMRI, the measured activations may reflect more complex cognitive processes that are active over longer periods and are thus not indexed by the aforementioned ERPs.

This problem is of high importance as the Cyberball paradigm is paramount to the study of ostracism, but to our knowledge, no systematic evaluation of ERP results has yet been conducted. Therefore, we conducted a systematic review of studies that employ the Cyberball paradigm in healthy adults to answer three questions: 1) Which ERPs are investigated in the Cyberball paradigm; 2) How do the ERPs change between conditions, throw types or interactions of condition and throw type; 3) Do the results support the idea of a specific neural alarm system for ostracism or do they reflect more fundamental neural processes elicited by characteristics and adaptations of the paradigm. Additionally, one meta-analysis regarding the P3b is conducted (receive - neglect). Results from this analysis are used to further answer the three aforementioned questions and to provide an estimate of expected effect sizes for ERP differences with regard to the Cyberball paradigm.

2. Materials and methods

This systematic review was conducted according to the guidelines of "The Preferred Reporting Items for Systematic Reviews and Meta-Analyses" statement (PRISMA, Moher et al., 2009). The research protocol was designed and registered in the PROSPERO database (registration number: CRD42021286595, registration date: November 21, 2021). The PRISMA flowchart is shown in Figure 2.

2.1. Search strategy

Three online databases (Embase, Pubmed and Web of Science) were searched for relevant papers concerning EEG and the Cyberball paradigm using the following search strategy: ("*EEG*" OR "*electroencephalography*" OR "*ERP*" OR "*event-related potential*") AND ("*ostracism*" OR "*social exclusion*" OR "*social inclusion*" OR "*social rejection*" OR "*Cyberball*").

2.2. Study selection

After searching the three databases, all papers were imported into EndNote to identify and remove duplicates automatically. Next, three independent reviewers (G.V. and L.G., G.V. and F.A.) screened the title and abstracts using the Rayyan software (Rayyan Systems, 2023). Afterward, the full texts of the remaining articles were assessed and articles were selected based on the in- and exclusion criteria. Studies were included if: 1) ERPs were recorded during a Cyberball game containing both an inclusion and an exclusion/overinclusion/re-inclusion condition; 2) data of adult, healthy, unmedicated participants with no (history of) psychiatric or neurological incidents or disorders were available; 3) patient populations were investigated, but data of a control group was available; 4) the paper was written in English. Studies were excluded if: 1) it involved testing animals or children; 2) it involved testing participants with psychiatric disorders and there was no data available of a control group; 3) only an abstract was available; 4) it was a (systematic) review article and/or meta-analysis, an editorial, a case report, a letter, or a conference proceeding. Articles published up to October 5th, 2022, were included. If only an abstract was found, the authors were contacted by mail, and if an article was written that adhered to the above-defined inclusion- and exclusion criteria, it was included.

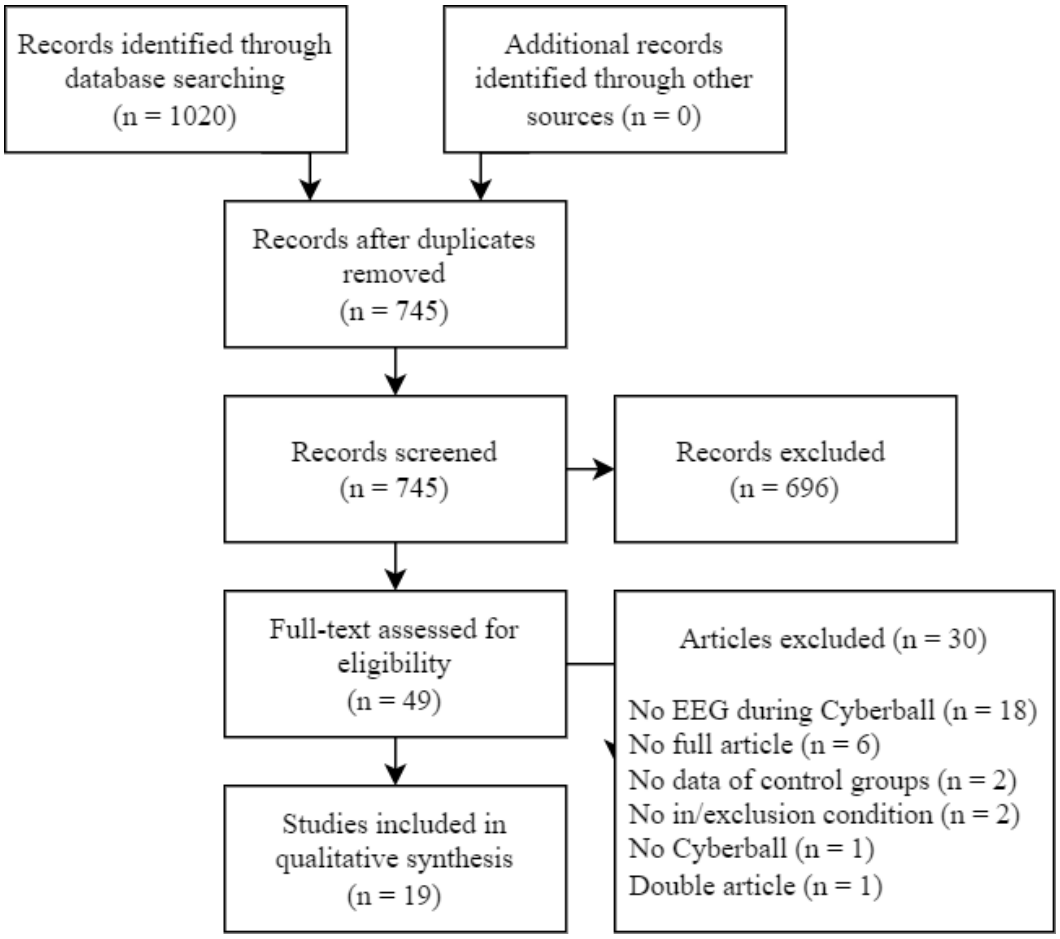

Figure 2: The PRISMA flow diagram (Moher et al., 2009).

2.3. Quality assessment

All included papers were evaluated according to an adapted version of the Standard Quality Assessment Criteria (SQAC) for Evaluating Primary Research Papers from a Variety of Fields (Kmet et al., 2004). This quality assessment tool consists of 14 questions regarding the validity, reproducibility, and comprehensibility of the included articles. Each question had three possible answers: *yes* (= 2), indicating that all necessary information is available; *partial* (= 1), meaning that some but not all necessary information was available; and *no* (= 0), indicating that no information is available. A total score was obtained for each article by summing the score for each question and dividing it by the highest possible score. The adjusted version of the SQAC and the reasoning behind each score for each question can be found in section 7.6.1.

2.4. Data extraction

Of the 19 papers that were included in this systematic review, the following data was extracted: *information about the paper* (i.e. title, DOI, first author and year of publication), *demographic information* (i.e. total number of participants, proportion men/women, mean age and standard deviation, age range, inclusion/exclusion criteria and recruiting method), *Cyberball information* (i.e. which design was used for the inclusion and exclusion manipulation, the cover story, the inclusion and exclusion probability, the time between throws, the time that the ball is in the center and the total amount of throws), *EEG recording information* (i.e. the amount of channels used, the placement method, the impedances, the sampling rate and the references), *EEG preprocessing information* (i.e. which filters were applied, whether or not they interpolated bad channels, whether or not they re-referenced the data, how artifacts were removed, the epoch start and end time, which ERP they studied and the time window in which they calculated that ERP), *ERP results* (i.e. over which channels the ERP was calculated and for each ERP whether or not the amplitude was (significantly) larger or smaller in one condition compared to the other) and *statistical information* (i.e. whether or not they performed a power calculation, a possible predetermined effect size, the power and alpha error probability). A summary of this information can be found in Table 1, the full information can be found on OSF (link: https://osf.io/dn5we).

2.5. Meta-analytic approach

The possibility for meta-analyses was assessed by counting how many times a specific ERP has been compared between two certain conditions (i.e., the difference between condition, the difference between throw types, or the difference between a condition-throw type interaction). If five or more studies described results for a specific difference (Tufanaru et al., 2015), the mean amplitude, the standard deviation, and the sample size was extracted. If data needed to be pooled to obtain a single mean amplitude and standard deviation, formula 1 and 2 were employed. In each formula, k denotes the total amount of studies and n_i denotes the sample size of study i. If the relevant data was not found in the article, the authors were contacted and if this information was not supplied, data was extracted from figures using *GRABIT*, a MATLAB toolbox developed for data extraction from figures (Doke, 2005). The meta-analyses were conducted using the Review Manager 5.4. and effect sizes were estimated using Hedges' g, which corrects effect sizes for small samples. Publication bias was estimated with an Egger's

test using the R programming language (version 4.2.2.; R Core Team, 2013). The data extraction process and corresponding values can be found on OSF (link: https://osf.io/9dvsp).

$$Mean_{pooled} = \frac{\sum_{i=1}^{k}(n_i mean_i)}{\sum_{i=1}^{k} n_i} \quad (1)$$

$$Variance_{pooled} = \frac{\sum_{i=1}^{k}(n_i-1)variance_i}{\sum_{i=1}^{k}(n_i-1)} \quad (2)$$

3. Results

3.1. Search results

After searching the databases, a total of 1020 potentially relevant articles were found (PubMed = 560, Web of Science 315, Embase = 145). 275 duplicates were identified in EndNote and subsequently removed, resulting in 745 articles of which the title and abstract were screened in Rayyan using the aforementioned in- and exclusion criteria (see section 2.2.). After the screening process, 696 articles were excluded and the full text of the 49 remaining articles was further inspected. 30 articles were further excluded (see Figure 2), leaving 19 articles that were included in the systematic review. The study selection process is depicted in Figure 2 and the characteristics of the included studies are shown in Table 1.

Table 1: Demographic information, paradigm information, and technical information regarding the ERP components of the included studies. **Legend:** $Ppts_{total, men}$ = total amount of participants, amount of male participants; *(M, STD)* = mean, standard deviation; *CB* = counterbalanced; *CS* = usage of a cover story, participants believed the confederates were real; *Thr.* = throw amount for a single condition; *Dur.* = duration of a single condition (unit: seconds); P_{excl} = probability of receiving the ball in the exclusion condition (0.33 is the probability of the inclusion condition); P_{other} = probability of receiving the ball in another condition than the exclusion condition; *Q* = questionnaires that were employed in the study; *Link* = analysis method that was employed by the study to compare changes in ERP component amplitudes with changes in questionnaires; CH_{sel} = method that is employed to select the channels; TW_{sel} = method that is employed to select the time windows; ERP_{comp} = method that is employed to compute the value representing the ERP component; *ERP* = ERP component that is studied; *Timing* = start and end time of the employed time window (unit: milliseconds); *N* = no; *Y* = yes; *I* = inclusion condition; *E* = exclusion condition; *OI* = overinclusion condition; *RI* = re-inclusion condition; *NTQ* = Need-Threat Questionnaire (Williams et al., 2000); *NM* = Negative Mood (subscale of the NTQ; Williams et al., 2000); *POI* = perceived ostracism intensity (subscale of the NTQ; Williams et al., 2000); *RSQ* = Rejection Sensitivity Questionnaire (Downey & Feldman, 1996); *ERQ* = Emotion Regulation Questionnaire (Gross & John, 2003); *EM* = self-reported emotions (Stemmler, 2009); *NTS* = Need-Threat Scale (Van Beest & Williams, 2006); *PANAS* = Positive And Negative Affect Schedule (Watson et al., 1988); *STAI* = State-Trait Anxiety Inventory (Spielberger et al. 1971); *BDI-II* = Beck Depression Inventory-II (Beck et al., 1996); *ES* = Emotion Scale (Staebler et al., 2009); *CORR* = correlation; *HRA* = hierarchical regression analysis; *MOD* = moderation analysis; *SA* = statistical analysis; *LIT* = previous literature; VIS_{GA} = visual inspection of the grand-averaged ERP; PL_{GA} = peak latencies of the grand-averaged ERP; A_{MAX} = maximal amplitude; *VIS* = visual inspection; T_{MAP} = topograhpic map; PA_{MAX} = peak amplitude (at peak latencies); *MA* = mean amplitude (unit: microvolt); *AUC* = Area Under the Curve (unit: microvolt*milliseconds); *PA* = peak amplitude (unit: microvolt); *CNV* = Contingent Negative Variation; *ECNV* = early-CNV; *LCNV* = late-CNV; *LPP* = Late Positive Potential; *Avg* = average; * = denotes the channel with the significant finding of the statistical analysis; ** = denotes the channels with the most significant findings of the statistical analysis, when multiple channels had significant results.

Author, Year	$Ppts_{total, men}$	Age (M, STD)	Paradigm Information						Technical Information							
			CB	CS	Thr.	Dur.	P_{excl}	P_{other}	Q	Link	CH_{sel}	TW_{sel}	ERP_{comp}	ERP	Timing	Channels
Fang, X., 2022	23 (3)	22.65 (5.1)	N	Y	200	420	0.17	-	NTQ NM	-	SA LIT	VIS_{GA}	MA	N2	140 – 220	Avg (Cz, Pz)
														P3b	300 – 400	Avg(Cz, Pz, P7, P8)
														P3b	400 – 500	Avg(Cz, Pz, P7, P8)
Gutz, L., 2011	20 (8)	25.4 (2.84)	Y	Y	200	-	0.16	-	NTQ NM POI	CORR	SA	VIS_{GA}	MA	N2	170 – 220	Fz, Cz, Pz*
														P3a	240 – 320	Fz, Cz*, Pz
														P3b	320 – 400	Fz, Cz, Pz*
Gutz, L., 2015	25 (3)	26 (4.44)	N	Y	200	420	0.16	-	NTQ RSQ	HRA	SA	VIS_{GA}	MA	P3b	310 – 390	Fz, Cz, Pz*
Ikeda, T., 2019	25 (22)	22.2 (2.74)	Y	N	I: 360 E: 124	-	0	-	NTQ	-	-	VIS_{GA}	MA	CNV	(-1000) – 0	FCz
														P3b	250 – 450	Avg (Cz, CPz, Pz)
Ikeda, T., 2021a	42 (25)	22.5 (2.84)	Y	N	280	-	-	OI: 0.46	NTQ	-	-	VIS_{GA}	MA	CNV	(-1000) – 0	Avg (FCz, Cz, CPz, Pz)
														P3b	320 – 400	Avg (Cz, CPz, Pz, Poz)
Ikeda, T., 2021b	33 (21)	22.3 (2.79)	Y	N	I: 360 E: 124	240	0	-	NM	-	VIS_{GA}	VIS_{GA} T_{MAP}	MA	ECNV	(-1000) – (-500)	FCz
														LCNV	(-500) – 0	Avg (Cz, CPz)
Jenkins, M., 2020	48 (16)	19.13 (-)	Y	Y	360	600	0.17	-	NTQ RSQ	-	PL_{GA} A_{MAX}	PL_{GA} LIT	MA (±40)	P3a	230 – 310	Cz
														P3b	310 – 390	CPz
Kawamoto, T., 2013	19 (8)	18.3 (-)	N	N	I: 135 E: 45	I: 450 E: 150	0	-	NTQ	CORR	-	PL_{GA} LIT	MA	P3b	350 – 450	Pz
Kiat, J., 2018	20 (10)	19.9 (1.37)	N	N	I: 104 E: 45	-	0.17	-	ERQ	MOD	LIT	LIT	MA	P3b	300 – 600	Pz
Niedeggen, M., 2014	40 (17)	24.75 (-)	Y	Y	200	420	-	OI: 0.46	NTQ NM POI	CORR	SA	VIS_{GA}	MA	N2	130 – 180	F3, Fz, F4, C3, Cz, C4, P3*, Pz*, P4*
														P2	150 – 210	F3*, Fz*, F4*, C3, Cz, C4, P3, Pz, P4
														P3b	320 – 400	F3, Fz, F4, C3*, Cz*, C4*, P3**, Pz**, P4**
Niedeggen, M., 2017	42 (20)	22.7 (-)	N	Y	200	420	0.16	-	NTQ NM	CORR	LIT	A_{MAX}	MA	P3b	320 – 400	Fz, Cz*, Pz*

Author, Year	$Ppts_{total, men}$	Age (M, STD)	Paradigm Information							Technical Information						
			CB	CS	Thr.	Dur.	P_{excl}	P_{other}	Q	Link	CH_{sel}	TW_{sel}	ERP_{comp}	ERP	Timing	Channels
Petereit, P., 2019	29 (0)	23.1 (2.63)	N	Y	I: 30 E: 120	-	0.16	-	EM	CORR	VIS LIT	LIT	AUC	LPP	800 – 1400	Pz
Themanson, J., 2013	22 (7)	-	N	Y	80	-	1-30: 0.33 30-80: 0	RI : 0.33	NTS NM PANAS	CORR	-	-	MA	N2	200 – 320	FCz
														P3b	320 – 450	Pz
Themanson, J., 2015	55 (26)	-	N	Y	156	-	1-85: 0.33 85-156: 0	-	PANAS STAI BDI-II NTS	CORR	LIT	-	MA	N2	200 – 320	FCz
														P3b	320 – 450	Pz
Weinbrecht, A., 2018	28 (4)	28.2 (5.81)	N	Y	200	420	-	OI: 0.45	NTQ NM	-	SA	VIS_{GA}	MA	P3b	310 – 390	Fz, Cz, Pz*
Weinbrecht, A., 2021	28 (-)	28 (5.64)	N	Y	200	420	-	OI: 0.45	ES	-	SA LIT	VIS_{GA}	MA	P2	160 – 225	Fz*, Cz, Pz
Weschke, S., 2013	15 (8)	24.7 (-)	N	Y	200	420	0.17	-	NTQ NM POI	-	SA LIT	VIS_{GA}	MA	N2	130 – 210	Fz, Cz, Pz*
														P3a	240 – 300	Fz, Cz*, Pz
														P3b	300 – 410	Fz, Cz, Pz*
Weschke, S., 2015	30 (16)	24.9 (-)	N	Y	300	600	0.17	-	NTQ POI	CORR	LIT	PL_{GA} PA_{GA}	PA	P3b	310 – 340	Pz
Weschke, S., 2016	15 (8)	24.7 (6.8)	N	Y	200	420	0.17	-	NTQ NM POI	CORR	SA	VIS_{GA}	MA	N2	100/130 – 170/210	Fz*, Cz*, Pz**
														P3a	240 – 300/320	Fz*, Cz**, Pz*
														P3b	300/320 – 400/410	Fz*, Cz*, Pz**

3.2. Quality assessment

Table 2 provides the scores of the quality assessment for all included papers. The mean total score across all articles is 77.3% (SD = 7.44; minimum = 59; maximum = 85). All papers did well at describing their research question (Q1). Almost all studies took care of interventional blinding by using an appropriate cover story (Q7) and did well at describing how they measured the ERP and how the Cyberball paradigm was implemented (Q8), reporting the results in sufficient detail (Q13), and making conclusions that are supported by the results (Q14). Overall, the question with the lowest score is Q9 (*Sample size appropriate?*), indicating that several studies did not manage to test a sufficiently large group of participants. Note that all papers received a score of 2 on Q5 and Q6 as Q5 evaluates participant group randomization and all studies employed a within-subject design and Q6 evaluates interventional blinding of the experimenter, which is impossible for studies employing the Cyberball paradigm. It should be noted that the scores were based on how these studies met the criteria in terms of answering our research questions, not their own.

Table 2: Risk of bias analysis for the included studies (Kmet et al., 2004)

Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total	Percentage
Fang, X. (2022)	2	2	2	2	2	2	2	2	0	1	1	0	2	2	22	76
Gutz, L. (2011)	2	1	1	2	2	2	2	2	0	1	0	2	2	2	23	79
Gutz, L. (2015)	2	2	1	1	2	2	1	2	0	1	0	0	2	2	19	65
Ikeda, T. (2019)	2	1	2	1	2	2	2	2	0	2	1	0	2	2	21	76
Ikeda, T. (2021a)	2	2	2	2	2	2	1	1	1	1	0	1	1	2	19	71
Ikeda, T. (2021b)	2	1	1	2	2	2	2	2	1	1	2	2	2	2	23	82
Jenkins, M. (2020)	2	1	1	2	2	2	2	2	1	2	1	1	2	2	22	85
Kawamoto, T. (2013)	2	2	2	2	2	2	2	2	0	1	2	2	2	1	24	85
Kiat, J. (2018)	2	1	1	1	2	2	1	1	0	1	0	0	2	2	15	59
Niedeggen, M. (2014)	2	1	2	1	2	2	2	2	1	1	0	2	2	2	21	74
Niedeggen, M. (2017)	2	1	1	2	2	2	2	1	1	1	1	1	2	2	21	76
Petereit, P. (2019)	2	1	2	1	2	2	2	1	0	1	2	2	2	1	20	71
Themanson, J. (2013)	2	2	2	1	2	2	2	2	0	1	1	2	2	2	23	79
Themanson, J. (2015)	2	2	1	1	2	2	2	2	2	1	1	1	2	2	20	79
Weinbrecht, A. (2018)	2	1	2	2	2	2	2	2	0	1	2	2	2	1	23	85
Weinbrecht, A. (2021)	2	1	0	1	2	2	1	2	0	1	0	2	2	2	18	65
Weschke, S. (2013)	2	2	2	2	2	2	2	2	0	1	1	0	1	1	20	71
Weschke, S. (2015)	2	1	2	2	2	2	2	2	1	1	2	2	2	2	26	85
Weschke, S. (2016)	2	1	1	2	2	2	2	2	0	1	1	1	2	2	23	76

3.3. Paradigm characteristics

In the included studies in the current systematic review the Cyberball paradigm was always employed, but differences with regard to how the paradigm was implemented are present. In this section, these implementation differences are discussed. Characteristics that differ significantly between included studies are included in Table 1.

3.3.1. Confederates

In all included articles the paradigm was implemented with two confederates. In one article a condition where the number of confederates was increased to five was also included, which was done to decrease the probability of receive throws compared to neglect throws without eliciting a feeling of ostracism in the participants (Weschke & Niedeggen, 2016). Given that this aspect does not differ significantly between studies, it is not included in Table 1.

3.3.2. Cover story

In fourteen studies a cover story where participants were told that the confederates were real was used (Fang et al., 2022; Gutz et al., 2011, 2015; Jenkins et al., 2020; Niedeggen et al., 2014, 2017; Petereit et al., 2019; Themanson et al., 2013,2015; Weinbrecht et al., 2018, 2021; Weschke et al., 2013, 2015, 2016). In five studies however the participants were informed that the co-players were not real but computer-generated (Ikeda & Takeda 2019, 2021a, 2021b; Kawamoto et al., 2013; Kiat et al., 2018).

3.3.3. Within/Between-subject design

The Cyberball can be investigated in either a within- (i.e., participants experience multiple conditions and contrasts for each participant are obtained) or between-subjects (i.e., participants only experience a single condition and comparisons between different groups are considered) design. In the current review, in several studies a between-subjects design was employed to investigate their own research questions (e.g., comparing healthy controls with individuals with borderline personality disorder (Gutz et al., 2015; Weinbrecht et al., 2018); investigating the influence of holding objects (Ikeda & Takeda, 2019, 2021a, 2021b); investigating the influence of oxytocin (Petereit et al., 2019)). The data that is extracted from the articles for this research however is always from participant groups that did experience all conditions of the paradigm, therefore considered coming from a within-subjects design.

3.3.4. Conditions

In all articles an inclusion condition was present, and in fifteen (out of nineteen) studies an exclusion condition was used. In four articles an overinclusion condition, where participants receive the ball more compared to the confederates, was employed (Ikeda & Takeda 2021a; Niedeggen et al., 2014; Weinbrecht et al., 2018, 2021). In one article a re-inclusion condition was used (Themanson et al., 2013) and in one article a control condition was also included, thus having an additional control aside from the inclusion condition (Kawamoto et al., 2013).

3.3.5. Throw probabilities

For the inclusion condition, in all studies a probability 33% for receive throws was employed. For the exclusion condition, three groups can be distinguished: those where *partial* exclusion was employed (probability of receive throw: 16-17 %; Fang et al., 2022; Gutz et al., 2011; Gutz et al., 2015; Jenkins et al., 2020; Kiat et al., 2018; Niedeggen et al., 2017; Petereit et al., 2019; Weschke et al., 2013, 2015, 2016), those where *total* exclusion was employed (Ikeda & Takeda, 2019, 2021b; Kawamoto et al., 2013), and those where the participant was initially included normally for a certain amount of throws, and subsequently excluded completely (Themanson et al., 2013, 2015). In all articles where the overinclusion condition was employed, the same probability was used (chance of receive throw: 45-46%; Ikeda & Takeda, 2021a; Niedeggen et al., 2014; Weinbrecht et al., 2018, 2021).

3.3.6. Condition duration & throw amount

Across the included studies, the duration of a single condition ranged from 2.5 minutes/150 seconds (Kawamoto et al., 2013) to 10 minutes/600 seconds (Jenkins et al., 2020; Weschke et al., 2015) and the amount of throws ranged from 30 (Petereit et al., 2019) to 360 (Ikeda & Takeda, 2019, 2021b; Jenkins et al., 2020).

3.3.7. Order of conditions

In thirteen studies a fixed order of conditions was used (i.e., the inclusion condition came first; Fang et al., 2022; Gutz et al., 2015; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2017; Petereit et al., 2019; Themanson et al., 2013, 2015; Weinbrecht et al., 2018, 2021; Weschke et al., 2013, 2015, 2016) while in six studies some form of counterbalancing was employed (Gutz et al., 2011; Ikeda & Takeda 2019, 2021a, 2021b; Jenkins et al., 2020; Niedeggen et al., 2014).

3.3.8. Self-report questionnaires

The behavioral effects of the Cyberball were assessed using a variety of self-report questionnaires across the included studies. The most commonly used is the Need Threat Questionnaire (NTQ; Williams et al., 2000) or the closeley related *Need Threat Scale* (NTS; Van Beest & Williams, 2006), which was employed in fourteen studies (Fang et al., 2022; Gutz et al., 2011, 2015; Ikeda & Takeda, 2019, 2021a; Jenkins et al., 2020; Kawamoto et al., 2013; Niedeggen et al., 2014, 2017; Themanson et al., 2015; Weinbrecht et al., 2018; Weschke et al. 2013, 2015, 2016). The NTS/NTQ has two additional subscales, one where negative mood (NM) is assessed, employed in nine studies (Fang et al., 2022; Gutz et al., 2011; Ikeda & Takeda, 2021b; Niedeggen et al., 2014, 2017; Themanson et al., 2013; Weinbrecht et al., 2018; Weschke & Niedeggen, 2013, 2016) and one assessing perceived ostracism intensity (POI), used in five studies (Gutz et al., 2011; Niedeggen et al., 2014; Weschke & Niedeggen, 2013, 2015, 2016). Aside from the NTQ/NTS, the *Rejection Sensitivity Questionnaire* (RSQ; Downey & Feldman, 1996) was used in two studies (Gutz et al., 2015; Jenkins et al., 2020), the *Emotion Regulation Questionnaire* (ERQ; Gross & John, 2003) in one study (Kiat et al., 2018), self-reported emotions (Stemmler, 2009; Staebler et al., 2009) in one study (Petereit et al., 2019), the *Positive And Negative Affect Schedule* (PANAS; Watson et al., 1988) in two studies (Themanson et al., 2013, 2015), the *State-Trait Anxiety Inventory* (STAI; Spielberger et al. 1971) in one study (Themanson et al., 2015), and the *Beck Depression Inventory-II* (BDI-II; Beck et al., 1996) in one study (Themanson et al., 2015). When an exclusion condition was employed in the study, significant increases in all employed questionnaires were reported compared to the inclusion condition by all studies, thus showing that the ERP-compatible Cyberball paradigm is capable to consistently evoke feelings of ostracism in participants. When an overinclusion condition was employed however, the results were less consistent: two articles reported significantly decreased threats, although not on all subscales (Ikeda & Takeda, 2021a; Niedeggen et al., 2014), while in one article no significant changes in positive emotions was found (Weinbrecht et al., 2021).

3.3.9. ERP-questionnaire comparisons

In several studies changes in ERP amplitudes across conditions were compared with changes in questionnaire scores (Gutz et al., 2011, 2015; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2014, 2017; Petereit et al., 2019; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015, 2016). The most commonly employed metric is correlation, whereby the changes in mean amplitude across conditions is correlated with changes in questionnaire scores, which was employed in nine studies (Gutz et al., 2011; Kawamoto et al., 2013; Niedeggen et al., 2014, 2017; Petereit et al., 2019; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015, 2016). In one study hierarchical regression analysis was used (Gutz et al., 2015), and in one study the link between self-report questionnaires and ERP data was explored using a moderation analysis (Kiat et al., 2018). Four ERP components were investigated through this method: the N2, P3a, P3b, and LPP. Almost all comparisons were obtained by comparing the inclusion and exclusion condition, as only one study investigated another condition: overinclusion (Niedeggen et al., 2014).

The N2 was linked with three questionnaires: the NTS, Positive affect (measured with the PANAS), and negative mood (measured with the NTS) but none of the correlations were significant (Gutz et al., 2011; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2016). The absence of significant correlations however does not contradict the notion of this component being part of a neural alarm system, as the first stage is assumed to be subconscious while self-reports reflect the conscious experience of the participants. The P3a was compared with the NTQ and negative mood (measured with NTS). In one article, negative mood was positively correlated with P3a amplitude changes (Gutz et al., 2011), but neither comparisons were significant in the other article (Weschke & Niedeggen, 2016). The P3b was compared with the NTQ, negative mood, positive affect (measured with PANAS), RSQ (both expectancy and anxiety), perceived ostracism intensity, and social rejection. The comparison with the NTQ was conducted eight times, where four studies found a negative correlation (Kawamoto et al., 2013; Niedeggen et al., 2017; Themanson et al., 2013, 2015), two studies found no significant correlation, where one study compared the P3b between an inclusion and overinclusion condition (Niedeggen et al., 2014) and one study compared the second half of the exclusion condition (Kawamoto et al., 2013), and two studies found unreliable links (Weschke & Niedeggen, 2015, 2016). Two studies looked into the link between the P3b and negative mood, where one study found a positive link (Niedeggen et al., 2017) and one study found unreliable results (Weschke & Niedeggen, 2016). Two studies compared the P3b with changes in positive

affect, twice finding a negative correlation (Themanson et al., 2013, 2015). One study investigated the moderating influence of cognitive appraisal on P3b changes, and found that higher appraisal resulted in higher P3b amplitudes during the exclusion condition. One study investigated two RSQ subscales in relation with the P3b, and found a significant negative correlation with the expectancy subscale and no significant correlation with the anxiety subscale (Gutz et al., 2015). Finally, one study compared P3b changes with perceived ostracism intensity and found a positive correlation (Gutz et al., 2011). Multiple correlations were found regarding the P3b, but their consistency remains somewhat limited given that some links (i.e., NTQ, negative mood) are not replicated across studies. Although this might be considered as evidence that this component is not related to ostracism, it should be mentioned that self-reports are collected after each condition, and sometimes only after both conditions. This time delay between the ERP data collection and self-report data collection might therefore obfuscate the possible relationship between both measures. The LPP component was compared with social rejection by one study, which reported a positive correlation (Petereit et al., 2019). An overview of the various comparisons can be found in section 7.6.7.

3.4. ERP characteristics

Aside from the differences regarding the implementation of the Cyberball paradigm, the technical steps taken to compute the ERP components also exhibit variations across studies. Three aspects will be discussed in this section: *channel selection* (i.e., on what basis were channels selected to compute ERP components), *time window selection* (i.e., how were the time windows defined in which the ERP component was computed), and *ERP computation* (i.e., how was the final value representing the ERP component computed). These can also be found in Table 1.

3.4.1. Channel selection

ERP components can be identified at multiple channels, and a variety of methods were used to select which channels are considered for their computation. A first method was the usage of previous literature to define the channel(s), which was employed in eight articles (Fang et al., 2022; Kiat et al., 2018; Niedeggen et al., 2017; Petereit et al., 2019; Themanson et al., 2015; Weinbrecht et al., 2021; Weschke et al., 2013, 2015). A second method was not selecting a channel a priori, but using a within-subjects factor *electrode* in the statistical analysis to investigate what channel(s) had the most significant ERP component contrasts across the considered dependent variable. This method was used in five articles (Gutz et al., 2011, 2015;

Niedeggen et al., 2014; Weinbrecht et al., 2018; Weschke et al., 2016), while in three other studies this method was combined with information from previous literature (Fang et al., 2022; Weinbrecht et al., 2021; Weschke et al., 2013). Two studies used visual inspection for channel selection: in one study channels were selected based on visual inspection of the grand-averaged ERP (i.e., the ERP waveform obtained by averaging ERP trials across all included participants for a specific event) (Ikeda & Takeda, 2021b), while in another study an ERP component in a channel was identified after the aggregation of only a few single trials (Petereit et al., 2019). In one article the peak latencies were firstly detected (i.e., the time duration between the presentation of the stimulus and the maximum value of the EEG signal within a predefined time window) for all included electrodes and subsequently the electrode with the maximum mean amplitude value at the peak latency was selected (Jenkins et al., 2020) for further analysis. For four studies, it was unclear how channel selection was done (Ikeda & Takeda 2019, 2021a; Kawamoto et al., 201; Themanson et al., 2013).

3.4.2. Time window selection

Given the variability both between- and within a single individual with regard to the latency of an ERP component (Luck, 2014), a time window (i.e., a predefined time range, commonly defined by a start and end time relative to the presentation of the stimulus, in which the ERP component is assumed to be present), is defined. The most commonly employed method here was visual inspection of the grand-averaged ERP (GA-ERP) waveform, which was employed in eleven studies (Fang et al., 2022; Gutz et al., 2011, 2015; Ikeda & Takeda, 2019, 2021a, 2021b; Niedeggen et al., 2014; Weinbrecht et al., 2018, 2021; Weschke et al., 2013, 2016). In one study the topographic map (i.e., a graphical visualization of the EEG activity across the scalp) of the ERP component of interest was considered aside from the GA-ERP waveform (Ikeda & Takeda, 2021b). In two studies peak latencies were used, combined with information from previous literature (Jenkins et al., 2020, Kawamoto et al., 2013) while in one study only previous literature was used (Petereit et al., 2019). In one study peak latencies were used for the ERP computation (Weschke et al., 2015). In one study the maximum amplitude for the selected channel(s) were computed to define time windows (Niedeggen et al., 2017). For two studies, it was unclear how the specific time window was selected, but time windows were mentioned in the introduction leading to the conclusion that these were defined based on previous research (Themanson et al., 2013, 2015).

3.4.3. ERP computation

Given the low signal-to-noise ratio of ERPs in individual trials (Luck, 2014), ERP components are computed from an average ERP waveform, obtained for each specific event of interest. In all studies average ERP waveforms were computed within each participant, and in almost all studies the mean amplitude of the predefined time window were computed to obtain a single value that characterizes the ERP component of interest for each participant (Fang et al., Gutz et al., 2011, 2015; Ikeda & Takeda, 2019, 2021a, 2021n; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2014, 2017; Themanson et al., 2013, 2015; Weinbrecht et al., 2018, 2021; Weschke et al., 2013, 2016). In one article the mean amplitude was computed, but in a participant-specific time window that was defined to be 40 milliseconds before and after the peak latency of each participant (Jenkins et al., 2020). In one other article peak amplitudes were used, rather than mean, as they used peak latencies and amplitudes for their time window selection (Weschke et al., 2015). Finally, in one article area under the curve (AUC) was used, which is the integration of the ERP waveform over the identified time window (unit: μV*ms) (Petereit et al., 2019).

3.5. Systematic review

The results of the current systematic review will be explained for each ERP specific and will be discussed in chronological order (i.e., the ERP with the shortest latency will be discussed first). For each ERP, results are divided into three categories: the main effect of *condition* (i.e., differences between the inclusion, exclusion, overinclusion, and re-inclusion blocks, regardless of throw type), the main effect of *throw type* (i.e., differences between receive and neglect throws, regardless of condition), and *interaction effects* (i.e., interaction effects between condition and throw types). Results will be discussed as changes in amplitude compared to either receive throws or the inclusion block, as these events can be considered the control condition of the Cyberball paradigm as no ostracism is present. When describing ERP components as smaller/larger, the amplitude of the ERP component is referenced. An overview of the results can be seen in Figure 3. The employed time windows within each study, grouped according to the investigated ERP can be seen in Figure 4.

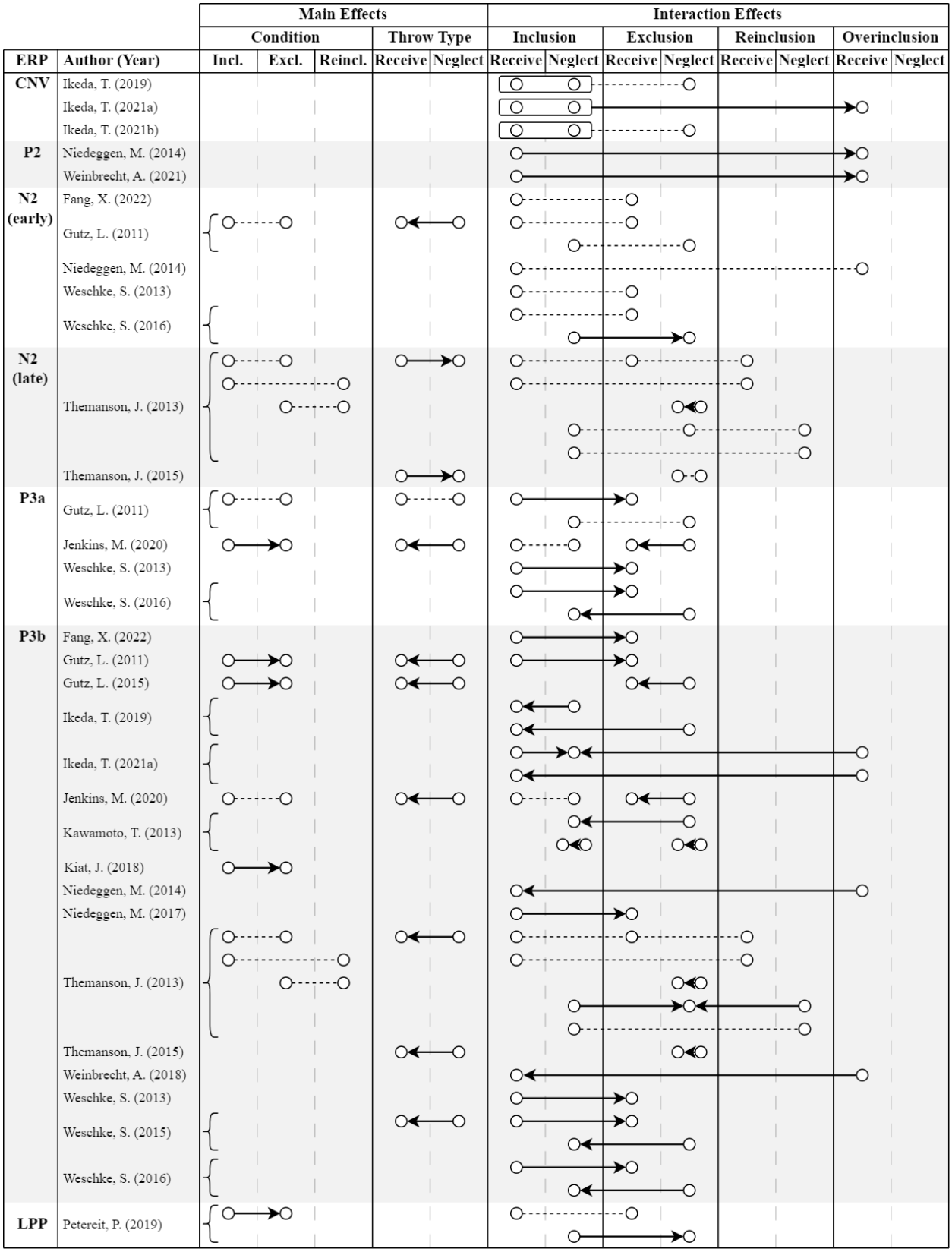

Figure 3: Overview of the results sorted by investigated ERP. **Legend:** Statistically significant results are indicated by full lines, with the arrow indicating the instance with the larger (regardless of polarity) ERP component amplitude. Statistically insignificant results are denoted by a dashed line. *Incl.* = Inclusion; *Excl.* = Exclusion; *Reincl.* = Re-inclusion; *CNV* = contingent negative variation; *LPP* = late positive potential.

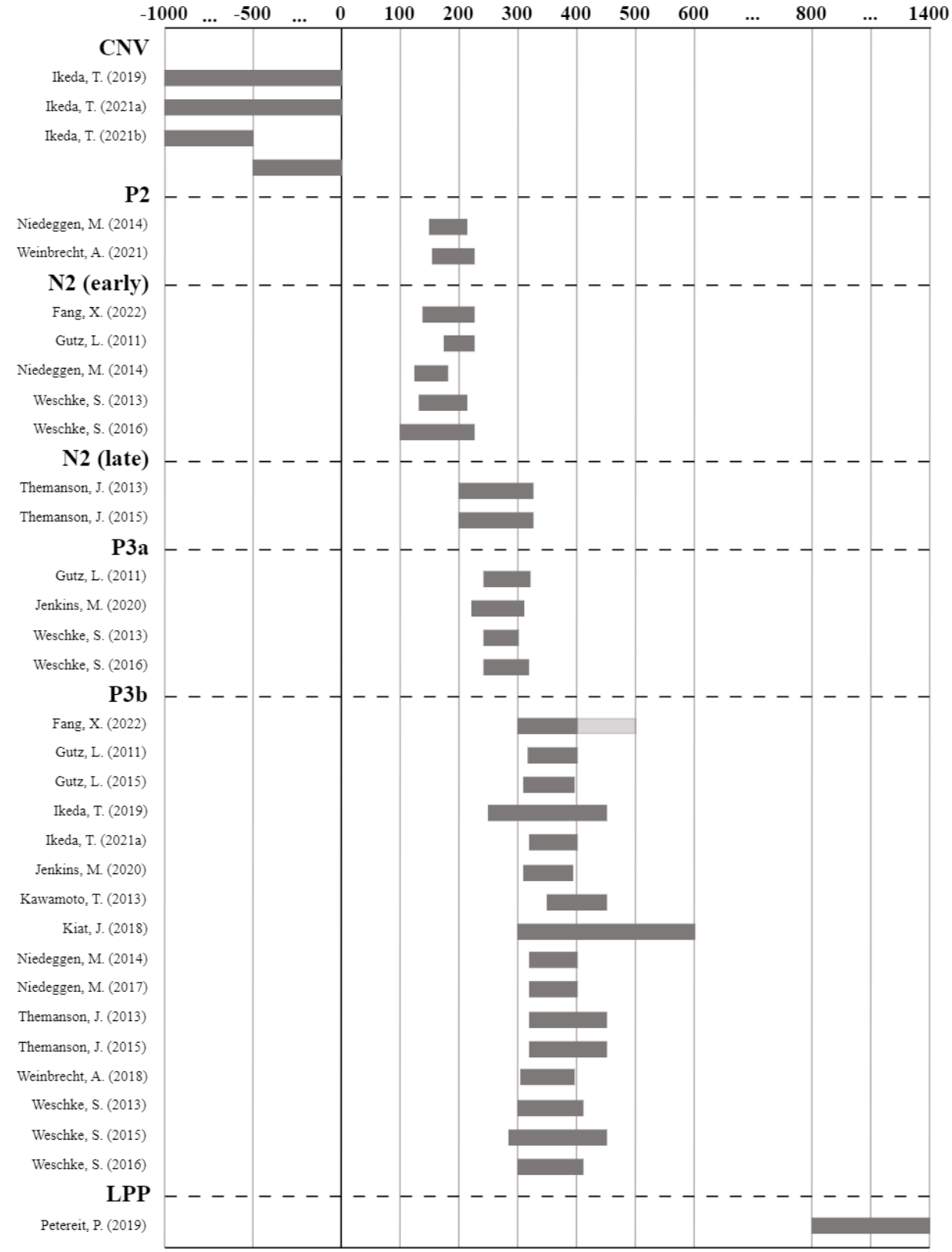

Figure 4: Employed time windows (unit: milliseconds) for each study, grouped by the investigated ERP. **Legend:** CNV = Contingent Negative Variation; LPP = Late positive potential. Notes: N2 (early) and N2 (late) only refer to the employed time windows, and have no further implicaton regarding the specific N2 component investigated. Fang. X. (2022) reports two results from the P3 component, the employed time windows are shown next to each other, with the second time window being slightly transparent.

3.5.1. Contingent negative variation (CNV)

The CNV has been investigated in three studies (Ikeda & Takeda, 2019, 2021a, 2021b). **Condition:** in two studies the CNV was compared between an inclusion (receive and neglect throws combined) and exclusion (only neglect throws) condition, but in neither of these studies a significant difference was found (Ikeda & Takeda, 2019, 2021b). In a third study the CNV was investigated during an inclusion (receive and neglect throws) and overinclusion (only receive throws) condition. A significantly larger (i.e., more negative) CNV was reported in the overinclusion condition (Ikeda & Takeda, 2021a). **Throw type:** in no studies the main effect of throw type was investigated. **Interaction:** in no studies interaction effects were investigated.

3.5.2. P2

In two studies the P2 was investigated (Niedeggen et al., 2014; Weinbrecht et al., 2021). **Condition:** in no studies the main effect of throw condition was investigated. **Throw type:** in no studies the main effect of throw type was investigated. **Interaction:** in both studies the difference for receive throws between an inclusion and overinclusion block was investigated and in both studies a significantly larger P2 for receive throws during the overinclusion block was reported (Niedeggen et al., 2014; Weinbrecht et al., 2021).

3.5.3. N2

In seven studies results from the "N2" were reported (Fang et al., 2022; Gutz et al., 2011; Niedeggen et al., 2014; Themanson et al., 2013, 2015; Weschke et al., 2013; 2016). Contrary to earlier and later discussed components, results from the N2 showed more variability with regard to both the time windows from which they were computed and the electrodes from which results were obtained (for an overview, see section 7.6.8.). Considering both aspects of the components, two groups could be delineated: an *early-N2* group measured between 100 – 220 milliseconds with a central-parietal maximum, investigated in five studies (Fang et al., 2022; Gutz et al., 2011; Niedeggen et al., 2014; Weschke et al., 2013, 2016), and a *late-N2* group measured between 200 – 320 milliseconds with a more frontal-central maximum (measured at FCz), reported on in two studies (Themanson et al., 2013, 2015). It should be noted that the indication of each group as either "early" or "late" is only based upon the difference in time windows, and has no implication on the possible N2 components that were most likely investigated. It should furthermore be mentioned that within the early-N2 group, results from one study could still be considered an outlier (Niedeggen et al., 2014), given that the employed time window has little overlap with the other time windows (see Figure 4).

3.5.3.1. Early-N2 Group

In five studies the N2 within a time window between 100 – 220 milliseconds was investigated (Fang et al., 2022; Gutz et al., 2011; Niedeggen et al., 2014; Weschke et al., 2013, 2016). **Condition:** in one study the difference between the inclusion and exclusion block was investigated, but no significant difference was found (Gutz et al., 2011). **Throw type:** in one study the main effect of throw type was investigated, and a significantly larger N2 for neglect throws was found (Gutz et al., 2011). **Interaction:** in four studies receive throws during the inclusion and exclusion condition were investigated, but no significant difference in N2 amplitude was found in any of these studies (Fang et al., 2022; Gutz et al., 2011; Weschke & Niedeggen, 2013, 2016). In two studies the neglect throws between an inclusion and exclusion block were compared. In one study no significant difference was reported (Gutz et al., 2011) and in one study a significantly larger N2 during the exclusion block for neglect throws was identified (Weschke & Niedeggen, 2016). In one study the receive throws between an inclusion and overinclusion block were compared, but no significant difference was found (Niedeggen et al., 2014).

3.5.3.2. Late-N2 Group

In two studies the N2 within a time windows between 200 – 320 milliseconds was examined (Themanson et al., 2013, 2015). **Condition:** in one study the difference between the inclusion, exclusion, and re-inclusion block was investigated, but no significant difference was found (Themanson et al., 2013). **Throw type:** in two studies the main effect of throw type was investigated (Themanson et al., 2013, 2015). In both studies a larger N2 for neglect throws was found. **Interaction:** in one study receive throws during the inclusion and exclusion condition were investigated, but no significant difference in N2 amplitude was found (Themanson et al., 2013). Themanson and colleagues (2013) further investigated the neglect throws between an inclusion and exclusion block and reported no significant difference, and examined the interactions of block type (inclusion, exclusion and re-inclusion) and throw type, but did not find any significant difference. **Other:** in two studies the 20 first and 20 last neglect throws during the exclusion block were compared (Themanson et al., 2013, 2015). In the first study it was reported that the 20 first throws elicited a significantly larger N2 (Themanson et al., 2013), but this result was not replicated in the latter study (Themanson et al., 2015).

3.5.4. The P3 complex

In sixteen studies (parts of) the P3 complex were investigated, making it the most studied ERP component within the Cyberball (Fang et al., 2022; Gutz et al., 2011, 2015; Ikeda & Takeda 2019, 2021a; Jenkins et al., 2020; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2014, 2017; Themanson et al., 2013, 2015; Weinbrecht et al., 2018; Weschke et al., 2013, 2015, 2016). Depending on the article, the P3 complex was either analyzed as one single component and referred to as the "P3" (Ikeda & Takeda, 2019, 2021a; Niedeggen et al., 2014, 2017, Weinbrecht et al., 2018), is defined as the "P3b" (Kawamoto et al., 2013; Kiat et al., 2018; Themanson et al., 2013, 2015; Weschke et al., 2015), or was analyzed by defining two adjacent time windows and two ERP components were extracted, referred to as the "P3a" and "P3b" (Gutz et al., 2011; Jenkins et al., 2020; Weschke et al., 2013, 2016). In one article two adjacent windows were defined, but the authors abstained from denoting them the P3a and P3b, but rather defined them as the "ascending" and "sustained" parts of the P3 and denoted that the sustained aspect was most likely reflecting the P3b (Fang et al., 2022).

The P3a and P3b components are commonly differentiated based on two aspects, their topographic distribution and latency (Polich, 2007). The P3a has a central maximum (around Cz) while the P3b has a parietal maximum (around Pz) (Polich, 2007). The P3a also has its maximum amplitude slightly earlier compared to the P3b (Polich, 2007), which explains the adjacent time windows employed in some studies that investigated both components. Based on these two criteria, the results have been divided into results that most likely reflected the P3a component, and those that likely reflected the P3b. A summary of all P3-related components and which component they likely reflect can be found in section 7.6.9.

3.5.4.1. P3a

In four articles results were reported that likely reflect the P3a component, given the employed time windows and reported maxima (Gutz et al., 2011; Jenkins et al., 2020; Weschke et al., 2013, 2016). **Condition:** in two studies the main effect of condition was investigated by comparing the inclusion and exclusion condition. While Gutz and colleagues (2011) did not find a significant effect, a significantly larger P3a was reported during the exclusion condition by Jenkins and Obhi (2020). **Throw type:** the same two studies where the main effect of condition was investigated, results regarding the main effect of throw type were also reported. Similarly to those results, Gutz and colleagues (2011) did not find a significant effect while a significantly smaller P3a was reported for neglect, compared to receive throws by Jenkins and

Obhi (2020). **Interaction:** In three studies receive throws between an inclusion and exclusion condition were investigated. In all three studies a significantly larger P3a for the receive throws during the exclusion condition was reported (Gutz et al., 2011; Weschke & Niedeggen, 2013, 2016). In two studies neglect throws between the inclusion and exclusion condition were further investigated. In one study no significant difference was found (Gutz et al., 2011), while in the other study a significantly smaller P3a for neglect throws in the exclusion condition was identified (Weschke & Niedeggen, 2016). Finally, in one study the difference between receive and neglect throws in the inclusion and exclusion condition was investigated separately. No difference was found within the inclusion condition, but the exclusion condition was accompanied by significantly smaller P3a amplitudes for the neglect throws (Jenkins & Obhi, 2020).

3.5.4.2. P3b

In sixteen studies results were reported that likely reflect the P3b component (Fang et al., 2022; Gutz et al., 2011, 2015; Ikeda & Takeda 2019, 2021a; Jenkins et al., 2020; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2014, 2017; Themanson et al., 2013, 2015; Weinbrecht et al., 2018; Weschke et al., 2013, 2015, 2016). **Condition:** in five studies the main effect of condition was investigated by comparing the inclusion with the exclusion block. In two studies no significant effect was found (Jenkins & Obhi, 2020; Themanson et al., 2013), while in three studies a significantly larger P3b in the exclusion condition was found (Gutz et al., 2011, 2015; Kiat et al., 2018). Themanson and colleagues (2013) compared the inclusion condition with an overinclusion (i.e., same throw probabilities as the inclusion condition, but after an exclusion condition) condition, but did not find a significant difference. Similarly, the exclusion condition was also compared with the re-inclusion condition, but no significant difference was revealed (Themanson et al., 2013). **Throw type:** in six studies the main effect of throw type was investigated, and in all six studies significantly smaller P3b amplitudes for neglect, compared to receive throws were found (Gutz et al., 2011, 2015; Jenkins & Obhi, 2020; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015). **Interaction:** in seven studies receive throws across conditions (inclusion, exclusion) were investigated. In six studies a significantly larger P3b for receive throws in the exclusion condition was found (Fang et al., 2022; Gutz et al., 2011; Niedeggen et al., 2017; Weschke & Niedeggen, 2013, 2015, 2016), while in one study no significant difference was found (Themanson et al., 2013). In four studies neglect throws between the inclusion and exclusion conditions were compared. In three studies significantly smaller P3b amplitudes during the exclusion condition were found (Kawamoto et

al., 2013; Weschke & Niedeggen, 2015, 2016), and in one study significantly larger P3b amplitudes were identified (Themanson et al., 2013). In three studies the differences between throw types in the inclusion condition were investigated. In one study a significantly larger P3b for neglect throws was reported (Ikeda & Takeda, 2021a), in another study the opposite effect was found (Ikeda & Takeda, 2019), while one found no significant differences (Jenkins & Obhi, 2020). In two studies the differences between the throw types in the exclusion condition was compared and twice a significantly larger P3b amplitude for receive throws was found (Gutz et al., 2015; Jenkins & Obhi, 2020). In three studies P3b amplitudes for neglect throws across the exclusion condition were compared by computing amplitudes for the first and second half of the exclusion block. In all three studies significantly larger P3b amplitudes for the first half were found (Kawamoto et al., 2013; Themanson et al., 2013, 2015). The comparison between the first and second half of a condition was also conducted for neglect throws during the inclusion condition. Similarly to the previous results, the P3b was significantly larger for the first half of the condition (Kawamoto et al., 2013). In three studies receive throws between an inclusion and overinclusion condition were investigated. In two studies significantly larger P3b amplitudes for the receive throws in the inclusion condition were found (Ikeda & Takeda, 2021a; Weinbrecht et al., 2018), while in one study the opposite effect was obtained (Niedeggen et al., 2014). In one study receive throws from the overinclusion condition were also compared with neglect throws from the inclusion condition, and a significantly larger P3b amplitude for the neglect throws was found (Ikeda & Tekada, 2021a). In one study, receive throws between an inclusion and re-inclusion condition were compared, but no significant difference was identified (Themanson et al., 2013). Themanson and colleagues (2013) further compared receive throws between the exclusion and re-inclusion condition, also revealing no significant differences. Finally, Themanson and colleagues (2013) compared neglect throws between the exclusion and re-inclusion condition, and found a larger P3b in the exclusion condition.

3.5.5. Late positive potential (LPP)

The LPP was investigated in one study (Petereit et al., 2019). **Condition:** a significantly larger LPP was reported during the exclusion block, compared to the inclusion block. **Throw type:** no results related to the main effect of throw type were reported. **Interaction:** the LPP was significantly larger for neglect throws during the exclusion, compared to neglect throws of the inclusion block. No significant difference for the receive throws between the inclusion and exclusion block were found.

3.6. Meta-analysis

After counting the number of times specific comparisons were reported in the included literature, two possible meta-analyses were identified. The main effect of condition for the P3b (six studies) and the main effect of throw type for the P3b (six studies). As only data from four studies were available for the main effect of condition, this meta-analysis was not conducted.

3.6.1. P3b : throw type

In six out of the nineteen included articles the main effect of throw type for the P3b was analyzed (Gutz et al., 2011, 2015; Jenkins & Obhi, 2020; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015). Unfortunately, data was not available from the paper of Gutz et al. (2011), so this study could not be included, resulting in 5 studies for this meta-analysis. Figure 5 shows the results of the meta-analysis. A significant effect size was found (SMD = 1.56, [0.87, 2.25]; Z = 4.44, p < 0.00001), indicating an increase in P3b amplitude for receive trials compared to neglect trials. Tests show that there is evidence for heterogeneity in the meta-analysis (t^2 = 0.53; chi^2 = 31.60, p < 0.00001; I^2 = 87%), but given the limited amount of included articles, no further subgroup analyses could be conducted. No publication bias was detected by the Egger's test (t = 1.281, p = 0.29, see supplementary materials (section 7.6.6.)), but this result should be considered with caution as the limited studies limit the power of this test.

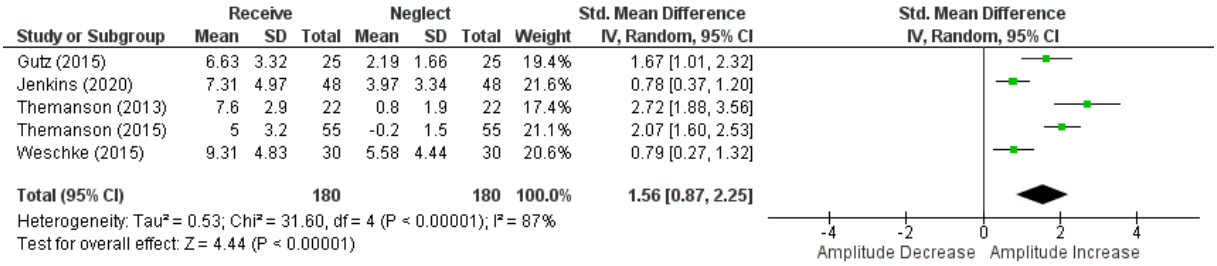

Figure 5: Forest plot illustrating the standardized mean differences (SMD), individual SMD, overall SMD, and heterogeneity statistics for the meta-analysis examining the main effect of throw type for the P3b.

4. Discussion

The Cyberball paradigm has been the center stage for the investigation of social ostracism. Since its inception by Williams and colleagues (2000), the paradigm has been extensively employed to investigate both the psychological (Hartgerink et al., 2015) and neural (S. Cacioppo et al., 2013; Mwilambwe-Tshilobo & Spreng, 2021; Wang et al., 2017) response to ostracism. One branch of the neural investigation into ostracism is the examination of short-term (order of milliseconds) neural mechanisms associated with processing ostracism-related information, indexed by event-related potential (ERP) components. Part of this research field has been synthesized, together with fMRI studies, into a model that might explain how the brain reacts to ostracism (Wang et al., 2017). This model eloquently proposes both where (through fMRI results) and when (through ERP results) ostracism-related information is processed within the brain but contains the assumption that the ERP components do in fact reflect ostracism-related processes. This assumption has been challenged in the past (and partly addressed in the article of Wang and colleagues (2017)), where research has shown that specific characteristics of the paradigm, such as differences in stimuli occurrence between conditions, might be the reason for the observed ERP effects, rather than the overarching social context of ostracism (Weschke & Niedeggen, 2015, 2016). The validation or rebuttal of the assumption that ERPs, evoked by the Cyberball paradigm, do in fact reflect ostracism-related processing is of great importance but has however not been assessed systematically.

Therefore, we systematically reviewed the ERP-Cyberball literature of healthy adult populations in an attempt to answer: 1) What ERP components have been investigated in the Cyberball paradigm; 2) How the ERP components change between conditions, throw types or interactions between condition and throw type; 3) If the results support the idea of a specific neural alarm system for ostracism or if they reflect more fundamental neural processes elicited by the characteristics of the paradigm. Our results indicate that overall, seven ERP components have been studied: the contingent negative variation (CNV), P2, N2, P3 (with subcomponents P3a and P3b), and the Late Positive Potential (LPP). We have split the results into three categories, being those that investigate the main effect of *condition* (i.e., comparing the inclusion and exclusion/overinclusion/re-inclusion condition), those investigating the main effect of *throw type* (i.e., comparing the receive and neglect throws) and studies that report on throw type-condition interactions (for an overview, see Figure 3). These results will be discussed in chronological order of the ERP-latency and the assumption of being reflective of

ostracism-related processing is assessed where possible. Of special interest are the ERPs that were included in the model of Wang and colleagues (2017) (i.e., P2, N2, P3a, P3b, and LPP).

4.1. Contingent negative variation (CNV)

The first ERP that is investigated is the CNV. This ERP component is, contrary to the other ERP components in this review, not elicited by the throws themselves but by a preceding stimulus that indicates an upcoming throw, without information of the direction of the throw. The CNV therefore is an index of anticipatory processes related to task execution, whereby a distinction can be made between the early CNV, linked with arousal, and the late CNV, linked with attention towards the task (Brunia et al., 2011). CNV amplitude changes have further been linked to the emotional valence (positive/negative) of the stimuli in some studies, where negative valence stimuli seem to attenuate CNV amplitudes while positive valence stimuli increase them (Hart et al., 2012; Ma et al., 2021).

Three articles investigated the CNV, with two articles comparing the inclusion and exclusion condition and reporting no significant changes (Ikeda & Takeda, 2019, 2021b), and one article comparing the inclusion with an overinclusion condition, reporting significantly larger CNV amplitudes in the overinclusion condition (Ikeda & Takeda, 2021a). Three important aspects of the studies should be considered when interpreting these results: (1) participants were aware that the confederates are not real, (2) participants rated the exclusion condition as more threatening (Ikeda & Takeda, 2019, 2021b) and the overinclusion as less threatening (Ikeda & Takeda, 2021a), and (3) during the exclusion condition participants did not receive the ball at all (i.e., total exclusion; Williams et al., 2000). Considering this, the absence of significant changes in the exclusion condition implies either that the individual throws were not deemed negative in the exclusion condition, which is difficult to reconcile with the fact that in both articles higher need threats and more negative mood after the exclusion condition were reported (Ikeda & Takeda, 2019, 2021b); or that the CNV is not affected by the overarching social context and only reflects anticipatory processes, which is also conflicting with the fact that no ball is thrown to the participants during the whole exclusion condition and minimal anticipation is thus expected. The increased CNV in the overinclusion condition on the other hand can be explained both from an anticipatory view and a valence view. As the ball is thrown more often in the overinclusion condition, more anticipation of throwing the ball by the participants themselves is present; likewise, because the overinclusion condition is viewed as less threatening, increased CNV amplitudes might reflect more positive valence in the

overinclusion condition. Combining both findings, however, it is challenging to conclude what exactly is reflected by the CNV. Although it might be possible that participants anticipate receiving the ball early in the exclusion condition, which, through the averaging of trials across the whole condition, results in a nonsignificant difference between the inclusion and exclusion conditions, it is also possible that each condition activates different neural mechanisms that influence the CNV in unique ways. Therefore, given the aforementioned aspects of the paradigms (i.e., total exclusion, no cover story) and the fact that only three studies in total investigated this component, no strong conclusion can be formed about whether this component is related to ostracism or paradigm characteristics and future research should further explore this ERP component.

4.2. P2

The second ERP is the P2, investigated in two articles (Niedeggen et al., 2014; Weinbrecht et al., 2021). Both articles report an increased P2 for receive throws during an overinclusion, compared to an inclusion condition, which is explained as the reflection of experiencing the overinclusion as more rewarding. This effect, however, is only found when the overinclusion condition comes after the inclusion condition (Niedeggen et al., 2014), and is believed to be related to an inability to experience overinclusion as rewarding if it is not preceded by a normal inclusion condition. Weinbrecht and colleagues (2021) further compared healthy controls with both patients with borderline personality disorder (BPD) and social anxiety disorder (SAD) and found that contrary to healthy controls and BPD patients, SAD patients did not have an increased P2 in the overinclusion condition, possibly because individuals with SAD are less capable of processing social rewarding stimuli correctly. Taken together, the P2 component seems to be an index of unpredicted (social) rewards during overinclusion in the Cyberball paradigm. This conclusion is not straightforward however, since Weinbrecht and colleagues (2021) report that the increase of P2 amplitude was not accompanied with an increase in positive emotions, which was expected and found in the earlier work of Niedeggen and colleagues (2014). Aside from this, the P2 was found to be increased for neglect throws in the exclusion compared to the inclusion condition in the model of Wang and colleagues (2017), where it was proposed that the P2 reflects the processing of salient stimuli needing attention, but this explanation is not able to explain the order dependence of the effect identified by both articles in the current review (Niedeggen et al., 2014; Weinbrecht et al., 2021). Considering the P2 as an index for unpredicted rewards might explain the increased P2 for exclusion throws found in the work of Wang and colleagues (2017), as being excluded could

be considered an unexpected negative reward. Additionally, Weschke & Niedeggen (2013) find evidence for a superimposed P2-like component for receive trials in the exclusion condition, only when real confederates are present in the room with the participants, and propose that this component could be the signal of a social reward, elicited when the context believability is high. The identification of this ERP component in other, non-social tasks such as gambling-like tasks or S1/S2 tasks (Holroyd et al., 2011; Potts et al., 2006), hints at the fact that this ERP component likely reflects unexpected rewards that are not specific to ostracism. This conclusion should however be considered with caution, as the comparison between the included studies and those in the article from Wang and colleagues (2017) is difficult to make given that different throw types and different conditions are used to obtain the results and the possibility that overinclusion, contrary to exclusion, evokes different neural mechanisms. Therefore future studies should further explore this component and how it is affected throughout the Cyberball.

4.3. N2

The third ERP is the N2, examined in seven studies (Fang et al., 2022; Gutz et al., 2011; Niedeggen et al., 2014; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2013, 2016). Given the large discrepancy regarding both the employed time windows and electrodes (see section 3.5.3. and section 7.6.8.) these results have been divided in two groups, those that evaluate an "early" N2 (Fang et al., 2022; Gutz et al., 2011, 2015; Niedeggen et al., 2014; Weschke & Niedeggen, 2013, 2016) and those that investigate a "late" N2 (Themanson et al., 2013, 2015). The N2 is assumed to be an index of the first, reflexive stage of the neural alarm system that is triggered by any exclusionary stimulus and reflects conflict monitoring (Donkers & Van Boxtel, 2004; Folstein & Van Petten, 2008; Larson et al., 2014; Yeung et al., 2004; Zadro, Wang et al., 2017; Williams & Richardson, 2004).

Results from the "late" N2 studies support this notion, whereby both studies report a significantly larger N2 component for neglect trials compared to receive trials (Themanson et al., 2013, 2015). This effect however does not seem to be specifically related to the overarching social context present in the different conditions, given that when throw types are compared across conditions no significant changes are found, no main effect of condition is identified, and no significant correlations are found between N2 amplitude changes and self-report questionnaires (Themanson et al., 2013, 2015). These results imply that the N2 component in the "late" N2 group likely reflects conflict monitoring, that reacts to any conflicting information, independently from the overarching social context present in the Cyberball

(Botvinick et al., 2001; Larson et al., 2014; van Veen et al., 2001). It should be noted here that this conclusion does not conflict with the need-threat model of Williams (2009) at all, as this model poses that ostracism is detected quickly, crudely, directly after a first indication, and is likely over-detected given that overdetection of ostracizing stimuli is preferable to underdetection (Williams, 2009).

Results from the "early" N2 group are less clearly in favor of the conflict monitoring hypothesis. While the investigated component similarly seems unrelated to the overarching social context, given the absence of a main effect of condition (Gutz et al., 2011), and mostly insignificant differences when throw types are compared across conditions (Fang et al., 2022; Niedeggen et al., 2014; Weschke & Niedeggen, 2013, 2016), some results cannot be explained by conflict monitoring or directly contradict the proposal. One article found an increased N2 amplitude for neglect throws in the exclusion, compared to the inclusion condition (Weschke & Niedeggen, 2016), which is not easily explained as both events are deemed conflicting. One article further found an increased N2 component for receive, compared to neglect throws, directly contradicting the idea of conflict monitoring (Gutz et al., 2011). These results imply that the "early" N2 group likely identifies a component not related to conflict monitoring, an implication that is strengthened by the reported central-parietal maximum (contrary to the fronto-central maximum of the "late" N2 component) and the employed time windows that cover an earlier timeframe than the commonly employed window for the N2 component linked with cognitive control and conflict monitoring (Folstein & Van Petten, 2008). This discrepancy is noted by Weschke & Niedeggen (2016), who additionally identified a similar component when participants were exposed to an oddball paradigm (Duncan-Johnson & Donchin, 1977) made to look visually similar to the Cyberball, with the same probabilities across conditions, but without the social context. Furthermore, Weschke & Niedeggen (2016) report that an N2 component is present for both receive and neglect throws, but that only in N2 components of neglect throws its amplitude is increased in the exclusion condition. They consequently conclude that the N2 component found for receive throws likely reflect either task relevance or target detection (explaining the increased amplitude for receive throws found in the study by Gutz and colleagues (2011)) while the N2 component found for neglect throws might indicate the inhibition of a prepared response, commonly found in go/no-go tasks (Folstein & Van Petten, 2008). The conclusion that the N2 for neglect throws is indicative of response inhibition should however be considered with caution for two reasons: the origin of the component in the go/no-go task has been linked with conflict monitoring rather than response inhibition (Donkers

& Van Boxtel, 2004) and paradigms examining response inhibition generally require speeded responses, which is not needed in the Cyberball. Taken together, it is as of yet not clear what process is reflected by the "early" N2 component and given that only one study explicitly reports the main effect of throw type, it is not clear whether every reported component in this group reflects the same process. Therefore future studies should investigate what process specifically is measured within this timerange.

4.4. The P3 complex

The subcomponents of the P3 complex, the P3a and P3b, are investigated by 16 studies, making it the most commonly examined ERP component within the Cyberball. Based on the topography and employed time windows, the results were divided into two groups: those that likely represent the P3a or P3b component (see section 7.6.9.). Based on this distinction, four studies were deemed to examine the P3a (Gutz et al., 2011; Jenkins & Ohbi, 2020; Weschke & Niedeggen, 2013, 2016), and all sixteen studies were deemed to investigate the P3b (Fang et al., 2022; Gutz et al., 2011, 2015; Ikeda & Takesa, 2019, 2021a; Jenkins & Ohbi, 2020; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2014, 2017; Themanson et al., 2013, 2015; Weinbrecht et al., 2018; Weschke & Niedeggen, 2013, 2015, 2016). The P3 complex is one of the most commonly investigated ERP components and has been investigated in a large variety of experimental paradigms. Converging evidence from these studies shows that the P3a and P3b components have distinct neural origins and functions, with the P3a originating from a frontal network that is stimulus-driven and related to attention, and the P3b stemming from more temporal-parietal neural activity linked with attention and memory processing (Polich, 2007). An important theory of the P3 components is the context-updating theory, which proposes that incoming stimuli are evaluated and compared to previous stimuli in working memory. If the stimulus is novel or different compared to previous stimuli, an update of the representation is required, which is indexed by the P3a and P3b. Here the P3a mainly reflects the attentional shifts due to the detection of novelty while the P3b mostly indexes the memory processing related to the model update (Polich, 2007; Polich et al., 2001). Consequently, stimuli that occur rarely will evoke a larger P3 complex. Wang and colleagues (2017) conclude that the P3 is enhanced during ostracism, with the P3a indexing induced negative mood and the P3b stimulus evaluation and categorization. While not conflicting with the context updating theory, Wang and colleagues (2017) link the P3 complex explicitly with the induction of negative emotions and appraisal. Aside from both proposals, another theory should be mentioned: *expectancy violation*, which posits that stimuli incongruent with the expectations of an

individual are deemed aversive and result in attempts to resolve the aforementioned incongruency (Proulx et al., 2012). Within this proposal, the P3 components can be seen as indices of adjustments to an internal model (conform to the context updating theory) but instead of being sensitive to objective probabilities of stimuli, adjustments are made according to the expected probabilities (Weschke & Niedeggen, 2015). Two notes should be made regarding the concept of expectancy violations: *1)* it does not contradict the context updating theory but provides additional avenues for investigating ostracism by manipulating the expectations of participants outside of the probabilities of the throw types (for examples, see Weschke & Niedeggen, 2015; Niedeggen et al., 2019), and *2)* is not specific to ostracism (Proulx et al., 2012).

4.4.1. P3a

The P3a component has been investigated in four studies (Gutz et al., 2011; Jenkins et al., 2020; Weschke & Niedeggen, 2013, 2016). The most consistent result for this component is an increase in amplitude for receive throws in the exclusion, compared to the inclusion condition, identified by three studies and identified by Gutz and colleagues (2011) as order dependent (Gutz et al., 2011, Weschke & Niedeggen, 2013, 2016). This finding aligns with both the model of Wang and colleagues (2017) given that the increased amplitude is found in the exclusion condition, and the idea of expectancy violations and stimulus probability changes as a fixed order is necessary to identify the change and the fact that receive throws are less likely in the exclusion condition. Support for the neural alarm system was initially identified by Gutz and colleagues (2011), who found that amplitude changes are positively correlated with negative mood, and linked this component with the reflexive stage of the neural alarm system given that the ACC has been identified as a neural generator of the P3a (Williams, 2009; Polich, 2008; Volpe et al., 2007). This correlation however has not been replicated by Weschke & Niedeggen (2016), who additionally compared the Cyberball to an Oddball paradigm and concluded that the changes in the P3a component can be uncoupled from the effects of ostracism and are likely driven by the aforementioned probability differences of receive and neglect throws across conditions and introduced expectancy violations related to the order of conditions (Weschke & Niedeggen, 2016). This explanation is partly strengthened by the earlier work of Weschke & Niedeggen, who showed that increasing the believability of the Cyberball by having real confederates present in the room did not influence P3a amplitudes (Weschke & Niedeggen, 2013). Other results also align better with the idea of probability and expectancy violations than an ostracism-specific alarm system: an increased P3a for receive, compared to neglect throws

in the exclusion condition, identified by Jenkins and colleagues (2020), can be explained by the fact that receive throws are less likely and are thus not expected when the participant is excluded. The absence of significant differences between both throw types in the inclusion condition (Jenkins et al., 2020) further implies that when probabilities of throw types are the same, no significant difference is identified. Additionally, an increased P3a for neglect throws in the inclusion compared to the exclusion condition (Weschke & Niedeggen, 2016) can be explained given the increased likelihood of this throw type in the exclusion condition. The main effect of throw type, whereby a larger P3a is found for receive throws (Jenkins et al., 2020) is difficult to reconcile with a neural alarm perspective, but might be explained from a probability context. Since throw types are aggregated across conditions when the main effect is considered, receive throws are less likely to occur in general (equal occurrence in the inclusion condition, less occurrence in the exclusion condition), possibly explaining the increased amplitude. The aforementioned results however should however be considered with caution as few studies have investigated these comparisons and non-significant results have also been reported (Gutz et al., 2011). Finally, the main effect of condition with larger P3a amplitudes in the exclusion condition (Jenkins et al., 2020) is easily explained within the model of Wang and colleagues (2017), while the effects of probability or expectancy are less clear for this comparison. It is possible that, given the equal probabilities of both throw types in the inclusion condition, P3a amplitudes are in general smaller in the inclusion condition compared to the exclusion condition, where the smaller probability of receive throws results in a larger P3a amplitude overall. Taken together, results regarding the P3a hint at the fact that the probability differences between throw types and condition, and subsequent expectancy violations, are more suitable to explain the ERP results, which is somewhat strengthened by the fact that the correlation between the P3a amplitude changes and self-report changes seems unreliable (Weschke & Niedeggen, 2016). However, as only a few studies report results related to this component, and even fewer studies computed correlations between amplitude changes and self-reports, no strong conclusion can be formed.

4.4.2. P3b

The P3b component has been investigated by sixteen studies (Fang et al., 2022; Gutz et al., 2011, 2015; Ikeda & Takeda, 2019, 2021a; Jenkins et al., 2020; Kawamoto et al., 2013; Kiat et al., 2018; Niedeggen et al., 2014, 2017; Themanson et al., 2013, 2015; Weinbrecht et al., 2018; Weschke & Niedeggen, 2013, 2015, 2016). Four trends can be found across these studies: *1)* a significantly larger P3b in the exclusion, compared to the inclusion condition (Gutz et al.,

2011, 2015; Kiat et al., 2018), *2)* a significantly larger P3b for receive, compared to neglect throws (Gutz et al., 2011, 2015; Jenkins et al., 2020; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015), *3)* a significantly larger P3b for receive throws in the exclusion, compared to the inclusion condition (Fang et al., 2022; Gutz et al., 2011; Jenkins et al., 2020; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015), and *4)* a significantly larger P3b for receive throws in the inclusion compared to the overinclusion condition.

The most consistent trend is the main effect of throw type, where six studies found a larger P3b for receive, compared to neglect throws (Gutz et al., 2011, 2015; Jenkins & Obhi, 2020; Themanson et al., 2013, 2015; Weschke & Niedeggen, 2015). This comparison has been further investigated in the meta-analysis, which identified a large effect size (Hedges' g = 1.56), indicating that this difference is highly significant. As already mentioned in section 4.1.1., this result can be explained when the overall lower probability of receive throws across conditions is considered, while it is difficult to align with the model of Wang (2017), as larger P3b amplitudes would be expected for neglect, not receive throws.

The second trend, increased P3b amplitude for receive throws in the exclusion, compared to the inclusion condition, identified by six articles (Fang et al., 2022; Gutz et al., 2011; Niedeggen et al., 2017; Weschke & Niedeggen, 2013, 2015, 2016) while one article found no significant differences (Themanson et al., 2013), can be explained by all theories equally well. One study reports a significant link between changes in P3b amplitudes for receive throws across conditions with changes in the NTQ scales and negative mood (Niedeggen et al., 2017), which aligns best with the model of Wang and colleagues (2017). Another study however found that rejection expectation, but not rejection anxiety explained a significant amount of variance of P3b changes for receive throws across conditions, hinting at the fact that expectations are more linked to this comparison than affective measures (Gutz et al., 2015).

The third trend, the increased P3b for the exclusion, compared to the inclusion condition, is less consistent with three studies reporting significant increases (Gutz et al., 2011, 2015; Kiat et al., 2018) and two studies finding no significant differences (Jenkins et al., 2020; Themanson et al., 2013). This trend is best explained within the model of Wang and colleagues (2017), and additionally supported as changes in amplitude for this comparison have been linked with perceived ostracism intensity (Gutz et al., 2011) and cognitive appraisal (Kiat et al., 2018). However, two studies correlated this comparison with the NTQ (Weschke & Niedeggen, 2015, 2016) or negative mood (Weschke & Niedeggen, 2016) and did not find any reliable correlation, making the link again less convincing.

The fourth trend is consistent across all three studies, which report a significantly larger P3b for receive throws in the inclusion compared to the overinclusion condition (Ikeda & Takeda, 2021a; Niedeggen et al., 2014; Weinbrecht et al., 2018). These results are easily explained when the probabilities and consequent expectancies of this throw type in both conditions are considered, while the model of Wang (2017) has no predictions regarding overinclusion.

Aside from these four trends, three additional comparisons have been reported multiple times, although these results are less consistent and contradict across studies. Firstly, neglect throws are compared across the inclusion and exclusion condition by four studies, with one study reporting increased amplitudes for neglect throws in the exclusion condition (Themanson et al., 2013) while three studies report the opposite effect (Kawamoto et al.n 2013; Weschke & Niedeggen, 2015, 2016). The increase of the P3b for neglect throws in the exclusion condition aligns with the model of Wang and colleagues (2017), and both studies report significant correlations between questionnaires and ERP changes for this comparison. Gutz and colleagues (2011) report that increases in P3b amplitudes correlate with increases in the NTQ while Themanson and colleagues (2013) report a significant correlation for this comparison and decreases in positive affect as well as increased threat of the control subscale of the NTS. Correlations were also computed by the three studies identifying the opposite effect, Kawamoto and colleagues (2013) report a significant correlation between social pain and the P3b and show that this effect is only present in the first half of the condition, but both articles by Weschke & Niedeggen (2015, 2016) did not find any reliable correlation. Secondly, three articles compared receive and neglect throws in the inclusion condition (Ikeda & Takeda, 2019, 2021a; Jenkins et al., 2020). Each study reports a different result: Ikeda & Takeda (2019) found increased P3b amplitudes for receive throws, Jenkins & Ohbi did not find a significant result, and Ikeda & Takeda (2021a) found increased P3b amplitudes for neglect throws. Given the inconsistency across studies and the fact that participants in the studies of Ikeda & Takeda were aware of the non-existence of the confederates, no conclusion can be formed regarding this comparison. Thirdly, two studies reported increased amplitudes for receive, compared to neglect throws, in the exclusion condition. These results contradict the model of Wang (2017) while aligning with the context-updating theory and expectancy violations. Finally, three studies investigated P3b amplitudes of a single throw type throughout a single condition. All three studies find that in the second part of each condition, P3b amplitudes are smaller than in the first part (Kawamoto et al., 2013; Themanson et al., 2013, 2015). Kawamoto and colleagues further showed that only

P3b changes in the first half of each condition were significantly correlated with changes in social pain. These observations (also once observed for the N2; Themanson et al., 2013) clearly show that the length of the Cyberball in ERP studies has an effect on the observed neural mechanisms, but the precise origin of these decreases is difficult to uncover, as habituation to repeated stimulus exposure (Rule et al., 2002), the depletion of self-regulating mechanisms related to attention due to social exclusion (Baumeister et al., 2002), or the update of the expectancies as the new probabilities become clearer all predict similar results and are not distinguishable with only the current results.

Taken together, similarly to other ERP components, no clear conclusion can be obtained about what processes exactly drive the P3b component in the Cyberball as various comparisons align better with different proposed theories. This ambiguity, however, is only present when these results are considered in isolation as several studies show converging evidence that the P3b is best explained within the theory of expectancy violations, which is conducted by neural mechanisms that are not specific to processing ostracism-related information. The fact that the expected, rather than objective, probabilities are the main driver of the P3b changes and that the neural mechanism is not specific to ostracism, is shown in seven studies (Fang et al., 2022; Gutz et al., 2015; Niedeggen et al., 2017; Weinbrecht et al., 2018; Weschke et al., 2013, 2015, 2016). Gutz and colleagues (2015) compared ERP results from healthy controls with both patients with borderline personality disorder (BPD) and social anxiety disorder. In the inclusion condition, it was found that BPD patients have an increased P3b compared to healthy controls, which is explained by the fact that BPD patients have altered processing regarding social information and a priori expect to be excluded, which is substantiated by the fact that this group also reported higher levels of ostracism in the inclusion condition. The receival of the ball therefore violated their inherent expectations of being excluded, consequently resulting in an increased P3b. Weinbrecht and colleagues (2018) also compared BPD patients with healthy controls, but now employed an overinclusion, rather than an exclusion condition, and replicated the increased P3b effect for patients with BPD. Additionally, Weinbrecht and colleagues (2018) show that both BPD and SAD patients experience the inclusion condition as more ostracizing compared to healthy controls, which is reflected in the enhanced P3b of both groups compared to healthy controls. Aside from considering patient populations, adaptations to the standard setup also provide convincing evidence for expectancy violations, which has been explored by Weschke & Niedeggen (2013, 2015, 2016). In their 2013 study, Weschke & Niedeggen compared the classical Cyberball with a setup where confederates were in the same room as

participants, thus increasing the believability of the paradigm. While participants did rate the cover story as more believable, no significant changes were found for the P3b between the classic Cyberball and the condition with confederates in the same room, showing that changes in the component are not necessarily related to how believable the exclusion is, but rather is driven by other mechanisms. In their subsequent study (Weschke & Niedeggen, 2015), the Cyberball was further adapted by comparing the exclusion condition with two confederates with a condition where the number of participants was increased from two to five. This condition has a similar probability of receiving the ball compared to the classical exclusion condition but imposes the expectation of lower receive throws without the feeling of ostracism. Results show that the increase in P3b amplitude was only found in the classical exclusion condition, thus indicating that this component does not reflect objective probabilities of events but rather indexes violations of expectations. Finally, Weschke & Niedeggen (2016) compared the Cyberball to a visually similar Oddball paradigm. While the Cyberball elicited feelings of ostracism, indexed by the NTQ, negative mood, and perceived ostracism intensity that were not identified in the Oddball condition, no significant differences regarding the P3b were found. These results thus imply that both the oddball and Cyberball rely on a similar neural mechanism, most likely expectancy violations and that this mechanism can be uncoupled from the feelings of ostracism commonly identified in self-reports. Finally, Niedeggen and colleagues (2017) adapt the Cyberball setup by manipulating the position of the avatar representing the participant. The Cyberball normally places the avatar below both participants (Williams, 2000). Research however has shown that vertical placement influences expected social power, with superior positions reflecting higher social power (Fischke, 1992). Considering this, it is reasonable to assume that when the avatar is placed above the confederates, an expectancy of greater social power is created while an inferior position of the avatar is perceived as less powerful. These differences in perceived social power subsequently modulate the expectations of social participation, which is reflected both in the P3b as well as self-reports. Participants with inferior avatars reported less need-threat increases and had less pronounced P3b amplitudes compared to participants with avatars located above the participants (Niedeggen et al., 2017). Finally, Fang and colleagues (2022) showed that pre-exposure to loss of control, which manipulates the expectancy of involvement in social interactions, reduced the P3b component, further providing evidence that this component indexes expectancy violations. Aside from these studies, two inconsistencies previously mentioned, (1) the increased P3b amplitude for neglect throws in the exclusion, compared to the inclusion condition identified by Themanson and colleagues (2013), and (2) the adaptation effect identified by Kawamoto and colleagues (2013) and Themanson

and colleagues (2013, 2015), can be explained from an expectancy violation perspective. Contrary to the other articles, where either partial exclusion (Weschke & Niedeggen, 2015, 2016) or total exclusion (Kawamoto et al., 2013) was employed, resulting in the expectation of being excluded, Themanson and colleagues (2013) started the exclusion condition by a short period of initial inclusion (33 throws) before excluding the participant completely for 50 throws. Given the induced expectation of continued inclusion, combined with the short exclusion period compared to the other studies, it is reasonable to assume that the increased P3b here reflects the violation of the expected continuing involvement which was not updated in the small amount of neglect throws that remained. Additionally, the adaptation processes, where the P3b amplitudes decrease throughout a single condition, had been identified in three studies but no clear underlying reason could be identified across studies (Kawamoto et al., 2013; Themanson et al., 2013, 2015). This effect has been investigated in several articles not included in the current review, where the classic Cyberball setup was manipulated to better understand the cause of this effect (Niedeggen et al., 2019, 2023; Schuck et al., 2018). Schuck and colleagues (2018) build upon the results of the 2017 study by Niedeggen and colleagues, where the vertical position of the avatar was manipulated. Within the framework of expectancy violations, adaptation processes reflect the updating of the expected probabilities of events, whereby smaller P3b amplitudes indicate that the presented stimuli are better aligned with the expectations of the individual as the participant has learned the new probabilities of events. Considering this, Schuck and colleagues (2018) hypothesized that participants with an avatar located inferior to the confederates (indicating low social power; Fischke, 1992) would adapt more quickly to being excluded than participants with a superiorly located avatar, as a lack of social power results in a quicker acceptance of exclusion. This hypothesis was confirmed as an adaptation of the P3b was identified when the avatar was located below the confederates, but not when the avatar was located above the confederates. Importantly, this effect was found for receive, not neglect throws, and across varying degrees of exclusion, making the proposal of P3b adaptation reflecting the reduction of attentional resources for exclusionary stimuli (Kawamoto et al., 2013) unlikely. Niedeggen and colleagues (2019) explore the adaptation effect further by only employing an inclusion condition, but now the decision of the participants to throw the ball to a specified confederate is sometimes overruled, thus taking away the perceived control of the participant, a social threat that is unrelated to social exclusion. This manipulation was used aside from the previously mentioned position of the participant's avatar and the results are similar to those found by Schuck and colleagues (2018). Participants where the avatar was placed above the confederates did not show an adaptation in P3b amplitude,

while this was identified in participants with an inferiorly located avatar. While these results align with the previously mentioned explanation of expectancy violations, this study additionally provides evidence for the proposal that the P3b component in the Cyberball reflects neural mechanisms that are not specific to ostracism (Niedeggen et al., 2019). Finally, Niedeggen and colleagues (2023) combine both ostracism and loss of control in the Cyberball by including a group where participants are both excluded and their intended throw direction can be overruled. Here the results show that when both threats are experienced together, the P3b is enhanced compared to the experience of a single social threat and no adaptation can be identified, while it is present when only one threat is employed. These results imply that the neural system responsible for the P3b in the Cyberball can be sensitized by the presence of additional social threats and that adaptation processes are delayed by concurrent threats (Niedeggen et al., 2023).

Considering the aforementioned research line (as well as the additional articles not included in the current review; see e.g., Niedeggen et al., 2019, 2023; Schuck et al., 2018), we conclude that in the Cyberball, the P3b indexes expectation violations and reflects a neural mechanism not specific to ostracism.

4.5. Late positive potential (LPP)

The last ERP is the LPP, investigated in one study (Petereit et al., 2019). Both a main effect of condition, with a larger LPP during the exclusion, compared to the inclusion condition, and a significantly larger LPP for neglect throws in the exclusion, compared to the inclusion condition, are reported. The LPP is linked with the (emotional) significance of stimuli (Hajcak & Foti, 2020). The results thus imply that both the larger context (i.e., condition differences) and stimulus-specific context (i.e., neglect throws between conditions) of ostracism are deemed more significant stimuli thus resulting in an increased LPP, a fact that is strengthened by the positive correlation between the LPP amplitudes and perceived social rejection. As only one study investigated the LPP, the interpretation should be considered with caution.

4.6. A specific neural alarm system?

Taking all results together and reflecting on the third research question (i.e., "do the results support the idea of a specific neural alarm system for ostracism, or do they reflect more fundamental neural processes elicited by the characteristics of the paradigm") leads to a the sobering conclusion that for most ERP components, aside from the P3b, no neural origin, ostracism-specific or not, can be reliably identified. This lackluster endpoint has several reasons that are related to the included studies, the Cyberball paradigm and its characteristics, and the research question itself.

A considerable "issue" regarding the included studies is the fact that they all have specific research questions, which logically influence both the specific ERP components that were investigated, as well as what conditions and throw types were considered in their analysis. For example, one article investigated the LPP and found consistent results that were strengthened by a significant correlation with perceived social rejection. As these are the only results, however, caution is required in their interpretation, and compared to components that were more commonly considered, no strong conclusion can be formed. Yet all included studies likely have data regarding the LPP but did not report them as this was not their intention. This bias goes both ways, as the most commonly researched component, the P3b, was investigated by researchers who were often specifically testing whether expectancy violations were the underlying factor or not. This does not discredit the conclusion that the P3b is mainly driven by expectancy violations, but this possible bias should still be considered, especially when small changes to the paradigm reveal significant alterations in the final results, as shown in the article by Themanson and colleagues (2013). Additionally, the selection of time windows for the computation of the ERP components is mostly done by visually inspecting the grand-averaged ERP waveform. This is a valid method of conducting ERP research (Luck, 2014), but has led to the necessary division of articles reporting on the N2 while the earlier mentioned bias of selecting throw types makes it difficult to conclude whether articles in the "early" N2 group find a similar component as only one article reported on the main effect of throw type (Gutz et al., 2011).

Aside from complications regarding the included studies, the Cyberball paradigm and its specificities should be considered as well. Changing the probability of receiving the ball is the central component of the paradigm, and is one of the simplest ways to reliably expose individuals to ostracism. Its adaptation for ERP research, however, leads to significant

complications as stimulus probabilities are highly influential on ERP components, and untangling what aspect specifically drives ERP components becomes thus much more complicated. Some studies have consequently adapted the classical Cyberball setup to evade this problem. Rather than comparing across conditions in a within-subjects design, between-subject comparisons are used that evade the confounding effects of probability, making it possible to investigate ERP components and additional aspects of ostracism (Fang et al., 2022; Niedeggen et al., 2017). Not all adaptations to the Cyberball paradigm have only negative consequences, however. The conversion to a within-subjects design combined mostly with a fixed order has led to insights regarding expectancy violations. In the 2018 study by Schuck and colleagues, it was shown that expectancy violations also hold for between-subject designs, identifying a commonality and core component of the Cyberball and ostracism that might not have been considered without the aforementioned conversion. It should be mentioned, however, that aside from the Cyberball additional paradigms have been developed that investigate highly similar concepts such as social rejection that address and mitigate possible confounding characteristics. One such example is the social rejection task (SJT) by Somerville and colleagues (2006). In the SJT, pictures of individuals are shown and the participant is asked whether they think the person would like them. After responding ("yes" or "no"), participants receive feedback either saying the person liked them or not. This paradigm mitigates three issues present in the Cyberball: it removes the ambiguity of when a participant is aware of the negative social context, it removes the differences of probability as participants are likes and disliked equally, and it provides a direct measure of expectancy violations independent of negative social feedback as the condition where participants thought they would not be liked but are liked violates the a priori expectations. It should be noted that the SJT does not induce ostracism, but rather social rejection which is closely related yet not the same (Williams, 2007). This should not be considered a limitation since, aside from the SJT task giving us the evidence that social feedback and expectancy violations are differentially processed in the ACC (Somerville et al., 2006), the usage of a single task in excess to investigate a psychological phenomenon results in a deep understanding of the task, but not necessarily the psychological phenomenon itself (Muscatell et al., 2021), a consideration that was already present in the initial article by Williams (1997).

Finally, a critical reflection should be made on the research question itself. The presence of a neural system that specifically detects exclusion-related stimuli is sensible from an evolutionary perspective, as the consequences are detrimental to the individual (both human

and non-human, Williams, 1997) with severe mental and physical complications as a consequence (Cacioppo, & Cacioppo, 2014; R. F. Baumeister & Leary, 1995; Rico-Uribe et al., 2018). Furthermore, on a behavioral level ostracism is a unique phenomenon that can be distinguished from closely related social concepts such as social rejection (Williams, 2007). The subsequent endeavor for the identification of this specific neural alarm system however is eerily similar to a common logical fallacy in neuroscience: reverse inference (Poldrack, 2006). In short, reverse inference refers to the reverse reasoning from neuroimaging data to cognitive or mental functions, where the activity of a certain region is taken as proof that this region is responsible for the cognitive function. While intuitively correct, this reasoning process only holds true if the region in question is only active during that specific mental or cognitive process. Considering this, the fact that the most consistent components in our review, the N2, the P3a, and P3b are found in a great variety of tasks across a large range of cognitive and emotional processes severely questions the possibility itself of any specificity towards a specific stimulus. This issue is additionally complicated by our understanding of ostracism, the temporal need-threat model (Williams, 2009). Williams (2009) concludes that ostracism is detected quickly, crudely, at the slightest representation, and is likely overdetected. Given these conclusions, predictions regarding ostracism are almost identical to those of conflict monitoring or expectancy violations. Even under the assumption that a specific neural alarm system is present, identifying it already proves highly difficult as predictions of multiple theories are almost identical. Of high importance here is that this does not invalidate the temporal need-threat model, nor does it deny the existence of an ostracism-specific neural alarm system, nor does it discredit previous studies that conduct research regarding ostracism using ERPs. It merely questions the fundamental assumption of whether, if present, we would be able to identify it. As already mentioned in the introduction, ERPs are small voltage fluctuations in the EEG signal mostly within a single second before or after a stimulus, with almost all components in this review lying between 0 and 500 milliseconds after stimulus presentation. Additionally, ERPs have a low signal-to-noise ratio making the averaging process across multiple events necessary. The first consideration already limits the possible cognitive or emotional processes that can be present while the second consideration eliminates a significant portion of present variability both within- and between individuals that might help to elucidate similar yet unique neural mechanisms. Based on this reasoning, the fact that the only reliable conclusion in this review, the P3b being an index of expectancy violations, shows that the identified ERP component is an index of a general cognitive function is not unexpected, it is the only logical conclusion.

5. Limitations

Two limitations should be mentioned regarding the current review. The first limitation is related to the in- and exclusion criteria. No data from patient populations were included in the current systematic review. This data might have provided additional insights into the third research question (i.e., “Do the results support the idea of a specific neural alarm system for ostracism or do they reflect more fundamental neural processes elicited by characteristics of the paradigm?”). The second limitation is related to the research questions of the included articles. Each study has a specific research question and hypothesis, which influences the selection of ERP components, throw types, and conditions that will be investigated. This might result in a biased reflection of ERP components in the Cyberball paradigm (e.g., the P2 component was only used in studies investigating overinclusion, not exclusion, making it difficult to make conclusions regarding this ERP component), as not all possible combinations of condition and throw type are present in the review.

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7. Supplemental information

7.1. Alterations from the published article

The final text above has some slight alterations from the published article in *Neuroscience & Biobehavioral Reviews.* None of the alterations are related to the substance, but are done for the presentation of the article in its current form. These alterations are :

- Figure 1 : font change.
- Figure 2 : font change and enlargment of words.
- Figure 3 : font change and enlargment of words.
- Figure 4 : font change and elargment of words.
- Text : throughout the text OSF links were provided for supplementary materials, these have been added below, and are referenced throughout the text.

7.2. Acknowledgments

We thank the reviewers for their constructive comments as the final article was significantly improved due to their feedback.

7.3. Funding

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7.4. Declaration of competing interest

The authors declare no conflict of interest.

7.5. Open practises statement

Supplementary data can be found online: https://osf.io/x4pa6

7.6. Supplementary materials

7.6.1. Risk of bias analysis – explanation of scoring

For this review, the questions were adjusted from the *Standard Quality Assessment Criteria for evaluating primary research papers from a variety of fields* (Kmet et al., 2004) to capture the specific technical aspects of EEG measurement and analysis.

Question 8 ("Outcome and (if applicable) exposure measure(s) are well defined and robust to measurement/misclassification bias? Means of assessment reported?") has been split up into two sub questions (8a: Outcome measure (EEG measure); 8b: exposure measure (ostracism))

Question 10 ("Analytic methods described/justified and appropriate?") has been split up into three sub questions (10a: EEG equipment information; 10b: preprocessing information; 10c: statistical analysis).

The final score for question 8 and 10 is calculated by employing the following rule: if all sub questions are reported completely the overall score is yes, if no sub question is answered the overall score is no and otherwise the overall score is partial.

Q1: Question/objective sufficiently described?

- Yes: study objective and research question(s) are sufficiently described
- Partial: study objective and research question(s) is mentioned, but is not completely clear or needs to be assessed from parts of the article other than the abstract or introduction
- No: study objective and research question(s) are not clearly described

Q2: Study design evident and appropriate?

- Yes: study design is appropriate for investigation of EEG changes due to ostracism
- Partial: Due to the study goal, which does not always align with the interest of this systematic review, the study design is not completely appropriate.
- No: Study design is not appropriate.

Q3: Method of subject/comparison group selection or source of information/input variables

described and appropriate?

- Yes: both the recruiting method as well as the reimbursement (if any) is given
- Partial: one of both is given
- Nothing is given

Q4: Subject (and comparison group, if applicable) characteristics sufficiently described?

- Yes: Both male-female amount and mean + std age is given
- Partial: one of the two is given
- No: neither is given

Q5: If interventional and random allocation was possible, was it described?

- Yes: randomization is mentioned and explained
- Partial: randomization is mentioned, but not explained
- No: not mentioned, not explained
- N/A: the study is a within-subjects design (this equals to a "Yes" (= 2))

Q6: If interventional and blinding of investigators was possible, was it reported?

- N/A: Since the goal of the studies is the induction of psychosocial stress, the investigators will always be aware of the paradigm and can therefore not be blinded. Therefore a score of "Yes" (=2) is always given

Q7: If interventional and blinding of subjects was possible, was it reported?

- Yes: A cover story is mentioned and the content of the cover story is given
- Partial: A cover story is mentioned, but not explained
- No: No cover story is mentioned

Q8: Outcome and (if applicable) exposure measure(s) well defined and robust to

measurement/misclassification bias? Means of assessment reported?

Q8a: Outcome measure

- Yes: the EEG measure and its calculation is described fully (channels, time-window)
- Partial: the EEG measure is mentioned, but it is not described how it is calculated
- No: EEG measure is not described

Q8b: Exposure measure

- Yes: the stressor is described fully (amount of throws, inclusion/exclusion probability, time between throws, time in center)
- Partial: the stressor is described, but not fully (no timing considerations etc.)
- No: the stressor is not descrbied

Q9: Sample size appropriate?

It is assumed that the investigation of stress can be approached as looking at the difference between two measurement times. Therefore a sample size of 50 is considered to be large enough to correctly investigate this research question. Sample sizes of 30+ will be considered as partially adequate.

Q10: Analytic methods described/justified and appropriate?

Q10a: EEG equipment information

- Yes: all important EEG equipment and recording information is described (channel amount, placement, impedance, sampling rate, reference)
- Partial: some variables are described
- No: no variables are described

Q10b: Preprocessing

- Yes: all important preprocessing steps are described (Filtering (LP, HP, Bandstop), rereferencing, artifact removal, epoch length)
- Partial: some variables are described
- No: no variables are described

Q10c: Statistical analysis

- Yes: statistical analysis is fully described (test statistic, test value, p value, multiple testing correction, effect size)
- Partial: statistical analysis is described, but not all important variables are given
- No: no statistics are described

Q11: Some estimate of variance is reported for the main results?

- Yes: Mean values with SEM or STDs are given
- Partial: Mean values with SEM or STDs are shown in figures
- No: No mention of SEM or STDs

Q12: Controlled for confounding?

- Yes: Considerable effort has been put into the elimination of possible confounders (male-female composition, no neurological/psychiatric disorders and/or no medication affecting the nervous system ...)
- Partial: Some effort has been put into confounding elimination, but important aspects are missing.
- No: Little to no effort has been put in confounder elimination

Q13: Results reported in sufficient detail?

- Yes: All mentioned measurements and outcomes are presented and explained in sufficient detail
- Partial: Quantitative results are explained for most outcomes, but some are missing or it is not clear which measures will be investigated specifically and no predictions are present
- No: One or several Outcomes are missing, no explanation of which outcomes will be investigated

Q14: Conclusions supported by the results?

- Yes: all conclusions are supported by the results
- Partial: Some conclusions are supported by the results, but some are not (eg. negative results are ignored etc.) OR no mention of the small sample size regarding the results isdiscussed
- No: Conclusions are not supported by the results

7.6.2. Risk of bias analysis – extended calculation

This supplemental material is an excel file with multiple headings, so it is not presented here. It can be found following the link provided in section 7.5.

7.6.3. Systematic review – extracted information

This supplemental material is an excel file with multiple headings, so it is not presented here. It can be found following the link provided in section 7.5.

7.6.4. Mata-analysis – data extraction procedure

Given the length of this supplemental material, and the fact that pictures from the included articles are present, it is not presented here. It can be found following the link provided in section 7.5.

7.6.5. Meta-analysis – numbers

This supplemental material is an excel file with multiple headings, so it is not presented here. It can be found following the link provided in section 7.5.

7.6.6. Meta-analysis – publication bias analysis

Funnel plots and Egger's test results (Egger et al., 1997) have been obtained using the R software language. The following R packages have been used to obtain the results: *meta*, *dmetar*. The code for the publication bias analysis can be found on the following OSF page: https://osf.io/um65z . It should be noted that the Egger's test might not have sufficient power to detect publication bias due to the relative small amount of studies in each meta-analysis (Sterne et al., 2011).

Reference for the Egger's test:

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *Bmj*, 315(7109), 629-634.

Reference for the Egger's test power:

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., ... & Higgins, J. P. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj*, 343.

7.6.6.1. P3b – receive-neglect meta-analysis

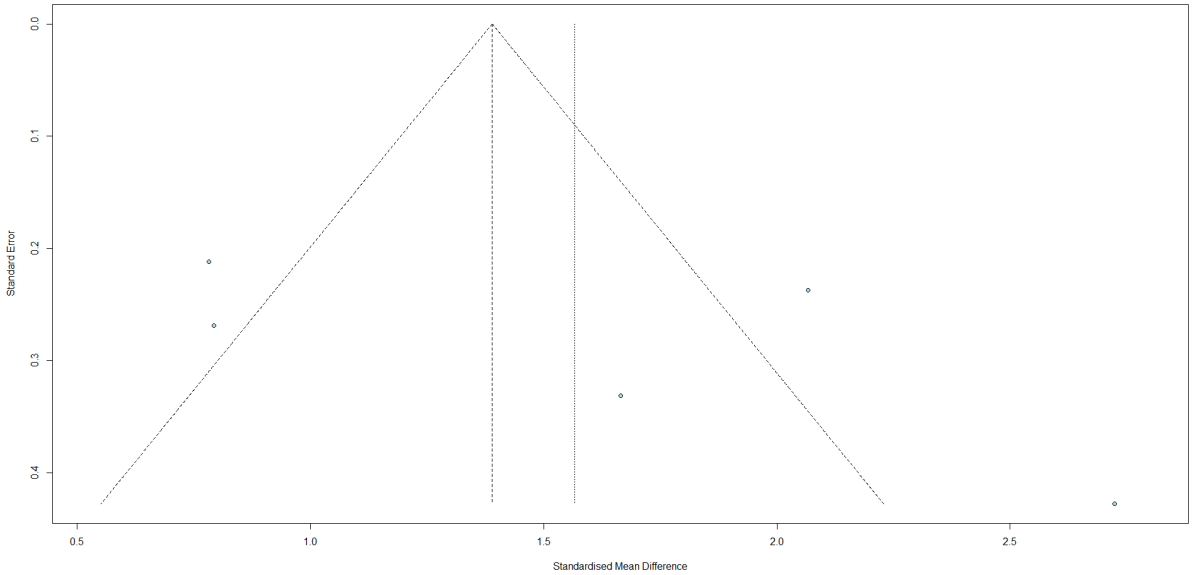

Figure (extra): Funnel plot of the P3b – receive-neglect meta-analysis.

Corresponding Egger's test results:

Intercept: 6.55

Lower bound (95% confidence): --3.47

Upper bound (95% cconfidence): --16.57

t-value: 1.281

p-value: 0.29

Conclusion:

The results of the Egger's test show no indication of a publication bias. In addition, no apparent funnel plot asymmetry is present.

7.6.7. ERP-Questionnaire comparison

Table (extra): overview of the examined comparisons between the ERP components and self-report questionnaires. **Legend:** *HRA*: hierarchical regression analysis. *Incl.*: inclusion. *Excl.*: exclusion. *NTS*: Need-Threat Scale (Van Beest & Williams, 2006). *POI*: perceived ostracism intensity (subscale of the NTQ; Williams et al., 2000). *NM*: negative mood (subscale of the NTQ; Williams et al., 2000). *RSQ*: Rejection Sensitivity Questionnaire (Downey & Feldman, 1996). *NS*: not significant. +: positive relationship. - : negative relationship.

Author, Year	Metric	Change	ERP	Questionnaire	Result
Gutz, 2011	Correlation	Incl. – Excl.	N2	NTS	NS
			P3a	NM	+
			P3b	POI	+
Gutz, 2015	HRA	Incl. – Excl. Receive	P3b	RSQ expectancy	-
			P3b	RSQ anxiety	NS
Kawamoto, 2013	Correlation	Incl. – Excl. Neglect	P3b First half	Social Pain	+
			P3b Second half	Social Pain	NS
Kiat, 2018	Moderation Analysis	Incl. – Excl.	P3b	Cognitive Appraisal	+
Niedeggen, 2014	Correlation	Incl. -OIncl.	P3b	NTQ	NS
Niedeggen, 2017	Correlation	Incl. – Excl. Receive	P3b	NTQ	-
		Incl. – Excl. Receive	P3b	Negative Mood	+
Petereit, 2019	Correlation	Incl. – Excl.	LPP	Social Rejection	+
Themanson, 2013	Correlation	Incl. – Excl. Neglect	N2	Positive Affect	NS
		Incl. – Excl. Neglect	N2	NTS control	NS
		Incl. – Excl. Neglect	P3b	Positive Affect	-
		Incl. – Excl. Neglect	P3b	NTS control	-
Themanson, 2015	Correlation	Incl. – Excl. Neglect	N2	Positive Affect	NS
		Incl. – Excl. Neglect	N2	NTS control	NS
		Incl. – Excl. Neglect	P3b	Positive Affect	-
		Incl. – Excl. Neglect	P3b	NTS control	-
Weschke, 2013	-	-	-	-	Not done, but mentioned
Weschke, 2015	Correlation	Incl. – Excl.	P3b	NTS subscales	Unreliable
Weschke, 2016	Correlation	Incl. – Excl.	N2	NTQ + NM	Unreliable
			P3a	NTQ + NM	Unreliable
			P3b	NTQ + NM	Unreliable

7.6.8. N2 group definitions

Table (extra): Assignment of N2 components according to their time windows and electrode-maxima.

Name, Year	Time Window	Electrodes	Maximum	Assumed Group
Fang, 2022	140 – 220	Cz, Pz	Average	1
Gutz, 2011	170 – 220	Fz, Cz, Pz	Pz	1
Niedeggen, 2014	120 – 170	Fz, F3, F4, Cz, C3, C4, Pz, P3, P4	Parietal	1
Themanson, 2013	200 – 320	FCz	-	2
Themanson, 2015	200 – 320	FCz	-	2
Weschke, 2013	130 – 210	Fz, Cz, Pz	Pz	1
Weschke, 2016	100 – 170	Fz, Cz, Pz	Cz (neglect)	1
	130 - 210	Fz, Cz, Pz	Pz (receive)	1

7.6.9. P3 complex group definitions

Table (extra): Assignment of the P3 components according to their time windows and electrode-maxima.

Author, Year	Time Window	Electrodes	Maximum	Assumed Group
Fang, 2022	300-400	Cz, Pz, P7, P8	Average	B
	400-500	Cz, Pz, P7, P8	Average	B
Gutz, 2011	240-320	Fz, Cz, Pz	Cz	A
	320-400	Fz, Cz, Pz	Pz	B
Gutz, 2015	310-390	Fz, Cz, Pz	Pz	B
Ikeda, 2019	250-450	Cz, Cpz, Pz	Average	B
Ikeda, 2021a	320-400	Cz, CPz, Pz, Poz	Average	B
Jenkins, 2020	230-310	Cz	-	A
	310-390	CPz	-	B
Kawamoto, 2013	350-450	Pz	-	B
Kiat, 2018	300-600	Pz	-	B
Niedeggen, 2014	320-400	Fz, F3, F4, Cz, C3, C4, Pz, P3, P4	Parietal	B
Niedeggen, 2017	320-400	Fz, Cz, Pz	Central, Parietal	B
Themanson, 2013	320-450	Pz	-	B
Themanson, 2015	320-450	Pz	-	B
Weinbrecht, 2018	310-390	Fz, Cz, Pz	Pz	B
Weschke, 2013	240-300	Fz, Cz, Pz	Cz	A
	300-410	Fz, Cz, Pz	Pz	B
Weschke, 2015	310-340	Pz	Pz	B
Weschke, 2016	240-300/320	Fz, Cz, Pz	Cz	A
	300/320-400/410	Fz, Cz, Pz	Pz	B

Chapter 4

Effects of acute psychosocial stress on source level EEG power and functional connectivity measures

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Abstract

The usage of EEG to uncover the influence of psychosocial stressors (PSSs) on neural activity has gained significant attention throughout recent years, but the results are often troubled by confounding stressor types. To investigate the effect of PSSs alone on neural activity, we employed a paradigm where participants are exposed to negative peer comparison as PSS, while other possible stressors are kept constant, and compared this with a condition where participants received neutral feedback. We analyzed commonly used sensor level EEG indices (frontal theta, alpha, and beta power) and further investigated whether source level power and functional connectivity (i.e., the temporal dependence between spatially seperated brain regions) measures, which have to our knowledge not yet been used, are more sensitive to PSSs than sensor level-derived EEG measures. Our results show that on sensor level, no significant frontal power changes are present (all p's > 0.16), indicating that sensor level frontal power measures are not sensitive enough to be affected by only PSSs. On source level, we find increased alpha power (indicative of decreased cortical activity) in the left- and right precuneus and right posterior cingulate cortex (all p's < 0.03) and increased functional connectivity between the left- and right precuneus ($p < 0.001$), indicating that acute, trial based PSSs lead to decreased precuneus/PCC activity, and possibly indicates a temporary disruption in the self-referential neural processes of an individual.

1. Introduction

Stress can be defined as the mental and physical reaction to personal or environmental stimuli that are deemed threatening to an individual (Folkman & Lazarus, 1984). Research has consistently shown that, when endured for a prolonged time, stress negatively impacts both the onset and progression of a variety of illnesses such as coronary heart disease, depression, and anxiety disorder (Daviu et al., 2019; Mazure, 1998; Sara et al., 2018; Tennant, 2001). Given this repeatedly reported link between stress and disease, a significant amount of research has been dedicated towards better understanding how stress affects individuals, and which stimuli lead to a stress response (Biondi & Picardi, 1999; Mauno et al., 2022). *Psychosocial stress* has been identified as one of the most important forms of stress throughout an individual's life given its strong link with the development of psychopathology (Dedoncker et al., 2021). Psychosocial stress, present in either unpredictable or uncontrollable social situations which are deemed unpleasant or threatening (Vanhollebeke et al., 2022), has obtained its prominent position due to the abundance of social interactions throughout daily life (Backé et al., 2012; Dedoncker et al., 2021; Siegrist, 2008; Vanderhasselt et al., 2015).

The role of the brain in the perception of stimuli as stressful and its reaction to stressors as the controlling agent of the following stress response has been a central focus of psychosocial stress research (Dedovic et al., 2009; McEwen, 2007, 2009). Initially, brain activity related to psychosocial stress has been studied mainly with functional magnetic resonance imaging (fMRI), and multiple brain regions have been identified that are involved in the psychosocial stress response. Cortical regions commonly found are the anterior insula (often coactive with parts of the inferior frontal gyrus such as the pars triangularis and pars opercularis), the anterior and posterior cingulate gyrus (ACC, PCC), the precuneus (often coactive with the PCC), and the orbitofrontal cortex (for various systematic reviews and meta-analyses, see Berretz et al., 2021; Cacioppo et al., 2013; Dedovic et al., 2009; Kogler et al., 2015; van Oort et al., 2017; Wang et al., 2017). Subcortical regions such as the (para)hippocampus, thalamus, lentiform nucleus, caudate nucleus, putamen, and amygdala are also consistently reported to be involved (Berretz et al., 2021; Dedovic et al., 2009; van Oort et al., 2017). Aside from fMRI, electroencephalography (EEG) has been employed increasingly throughout recent years for the investigation of psychosocial stress-related brain activity. Our recent systematic review identified a total of 13 EEG measures that have been employed in psychosocial stress research (Vanhollebeke et al., 2022). Most commonly employed is frontal alpha asymmetry (with conflicting results between studies), alpha power (which decreases significantly due to

psychosocial stressors), and beta power (which generally increases, although not significantly in our meta-analysis). Less commonly utilized measures are other power measures such as delta, theta, and sigma power, power ratios (the combination of power values from spatially distinct electrodes or from different frequency bands) and functional connectivity (FC, the study of temporal dependence between spatially distinct neural events; Friston, 1994) measures (Vanhollebeke et al., 2022). EEG is also increasingly used for the detection of mental stress with machine learning, again showing the rise of this neuroimaging technique in stress research (Katmah et al., 2021).

A variety of neuroimaging-compatible paradigms have been developed for the investigation of psychosocial stress. Although all paradigms employ a psychosocial stressor (e.g., negative feedback and peer comparison in the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005), social exclusion in the Cyberball paradigm (Williams et al., 2000) or social-evaluative threat in the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), these psychosocial stressors are often accompanied by other stressors such as cognitive stressors (e.g., imposed time limits or task demands). This co-occurrence of stressor types makes it difficult to directly link the measured neural activity to the unique social aspect of the employed paradigm. Research has shown that different psychosocial stress paradigms evoke different neuronal responses from individuals (Berretz et al., 2021), and a significant amount of research is being conducted for the development of EEG-based systems for the detection of psychosocial stress (Katmah et al., 2021), so any ambiguity in neural activity changes due to co-occurring stressor types needs further clarification.

In a recent article, Ehrhardt and colleagues (2021) have explicitly investigated the contribution of various individual stressor types (cognitive effort, time pressure, and social-evaluative threat) to changes in alpha and beta band power of frontal electrodes (F7, F3, Fz, Fpz, F4 and F8). The sobering results from their analysis have shown that the employed psychosocial stressor (social-evaluative threat, the fear of being judged negatively; Dickerson, 2008) does not significantly alter power in either the alpha or beta band, indicating that results attributed to the social component of a stress paradigm instead seem to reflect changes in cognitive processing (Ehrhardt et al., 2021).

Although this implication is highly significant for the research field, psychosocial stress may be detectable by other EEG measures than frontal alpha or beta power. Sensor level-derived EEG measures are known to be affected by volume conduction, understood as the spreading of electrical signals from a single brain source throughout the head (Nunez et al.,

2019; Schaworonkow & Nikulin, 2022). Psychosocial stressor-induced neural changes might therefore not be sufficiently registered by sensor level-derived EEG measures or can be overpowered by other spontaneous brain activity (Cohen, 2014). The usage of EEG source imaging, which projects the signals measured at the electrodes back to the neural sources within the brain (Michel & Brunet, 2019), and the corresponding source space is therefore of special interest. Aside from source level power measures, functional connectivity measures might also capture changes induced by psychosocial stressors and thus give more insight into the neuronal psychosocial stress response.

To investigate whether purely psychosocial stressors affect source level-derived EEG indices, we developed a paradigm where participants were exposed to a psychosocial stressor while keeping co-occurring stressors such as time pressure or task demands constant between both conditions. Participants were instructed to solve Raven's matrices of different levels of difficulty (Raven & Court, 1938). After each matrix, participants received (comparative) feedback which was manipulated to induce psychosocial stress. In the control condition, participants received neutral feedback (i.e., the participant performs on par with other individuals), and in another condition, the negative condition, negative feedback (i.e., the participant performs (progressively) worse than other individuals). Time limits were kept equal between both conditions and to further eliminate possible interferences of the task itself, and only data collected during the feedback exposure were analyzed. To evaluate whether the applied stressor was successful in eliciting a stress response, electrocardiography (ECG) data and state questionnaires, self-assessment manikins (SAM; Bradley & Lang, 1994), were also collected throughout the study. The SAM contains two scales: arousal (degree of activation due to the stimuli, from low to high) and valence (experienced emotional reaction to the stimuli, from negative to positive).

The research questions of the current study are threefold. Firstly, we investigated whether the psychosocial stressor elicits a physiological and mental response from the participants. We hypothesized that in the ECG signal, similarly to other psychosocial stressors, we would find an increase in sympathetic reactivity, identified by an increased heart rate acceleration, during the negative-, compared to the control condition (Kudielka et al., 2004; Taelman et al., 2009; Vrijkotte et al., 2000). We further hypothesized that in the SAM, in line with prior research, an increase in the arousal scale and a decrease in the valence scale would be found (Kuppens et al., 2013). Secondly, we tried to reproduce the results found by Ehrhardt and colleagues (2021) and therefore computed frontal theta, alpha, and beta power at the sensor

level, and compared the negative to the control condition. We hypothesized that similar to those results, no changes in these commonly used EEG measures due to a psychosocial stressor alone would be found . Finally, we investigated whether the purely psychosocial aspect of a stressor would be effective enough to affect source level-derived EEG measures. Therefore, we investigated the cortical regions commonly found in fMRI research (i.e., the anterior insula, ACC, PCC, precuneus, and orbitofrontal cortex; see above) and computed both their band power (theta, alpha, and beta) and the functional connectivity between them. Functional connectivity was estimated using amplitude envelope correlation (AEC), a robust connectivity measure (Colclough et al., 2016; Hipp et al., 2012). Given previous fMRI research, we hypothesized an increase in beta power in the anterior insula and an increase in alpha power in the precuneus and PCC (Berretz et al., 2021). We had no specific directional hypotheses regarding the functional connectivity estimates.

2. Materials and methods

2.1. Participants

A convenience sample of eighty-three healthy, Dutch-speaking individuals was recruited from the general population through internet postings on social media. All participants were right-handed, had no personal or familial history of epilepsy, have not had any neurosurgical procedure throughout their life, did not have any psychiatric-, neurological-, substance abuse-, heart-, respiratory-, or eye disorder in their life, had no metal or magnetic objects in their body or brain, were not using any psychoactive medication and had no skin conditions at the level of the head (see section 7.6.1. for all exclusion criteria). All participants refrained from caffeine and nicotine in the two hours leading up to the experiment. Data was collected between 10 a.m. and 5 p.m. Data from 10 participants was not used (two participants had incomplete data, and eight participants were excluded due to insufficient EEG data quality based on visual inspection or remaining epoch amount after artifact rejection), resulting in a final dataset of 73 participants (47 females, M_{age} = 22.8, SD_{age} = 5.3, Age range = 18-47 years). The experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethical Committee of the Ghent University Hospital (registration number: B670201940636). Participants received €30 for their participation.

2.2. Experimental procedure

2.2.1. Study paradigm

Before in-person data collection, participants gave their informed consent and filled in trait questionnaires (this study is part of a larger project, and these trait questionnaires are not further discussed in this article) through the online platform Limesurvey (Schmitz, 2012). In-person data was collected in a dedicated room at the Department of Neurology at the Ghent University hospital. Upon arrival, participants gave their written consent again (on paper), after which the EEG and ECG electrodes were applied (total duration between 20 and 45 minutes). After electrode placement, participants were seated in a chair in front of a computer monitor (Dell E2216H) at a distance of around 60 cm and were told to remain seated and move as little as possible to reduce the presence of motion artifacts in the data. Instructions and tasks for the experiment were given using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) and the SAMs were collected using a custom app on a tablet (Huawei MediaPad M5).

After the introduction and electrode placement, participants rested for 10 minutes with closed eyes (habituation), after which they filled in a SAM questionnaire (see section 2.2.4.). Following the initial resting period, the control condition was presented. In the control condition, participants solved a series of Raven's matrices (see section 2.2.2.) in three blocks, with each block either lasting six minutes or ending when the participant solved all 11 matrices assigned to the block. After each block, participants filled in a SAM. After the control condition, participants rested again for 10 minutes (followed by a SAM) after which the negative condition was presented. The negative condition was identical to the control condition, aside from a manipulation during the feedback (see section 2.2.2.). After the negative condition, participants rested for a third time for 10 minutes (followed by a final SAM), after which they were debriefed about the goal of the study, and payment information was collected. The study paradigm is shown in Figure 1.

2.2.2. Trial and feedback

In both the control and negative condition, participants were instructed to solve Raven's matrices. Raven's matrices are a visual exercise where eight figures are presented in a 3 x 3 raster with an empty space in the lower right part of the raster (see Figure 1, bottom for an example). The goal of the exercise is to select the ninth figure (from 8 possibilities) which completes the raster by identifying the pattern shared by the eight initially shown figures (Raven & Court, 1938). Shown above the Raven's matrix was a countdown timer, which showed the time left to solve the Raven's matrix in seconds. Three levels of difficulty were defined for the Raven's matrices and the allowed time to solve each problem depended on the difficulty of the individual matrix (20 seconds for easy, 45 seconds for medium, and 100 seconds for difficult; see OSF (link: https://osf.io/py63g) for further information regarding the Raven's matrices). Participants solved the matrices by pressing a number between 1 and 8 with their right hand on the keyboard Numpad, corresponding to one of the eight possible solutions. When the Raven's matrix ended (either through a response of the participant, or a time-out) a feedback screen consisting of three components was shown for six seconds. The first component (*top*) was a three-colored (red, yellow, green) comparison bar containing two arrows indicating 1) the individual and 2) the average performance of a comparison group; the second component (*center*) was a single word indicating the evaluation of the participant's response ("correct!", "incorrect!" or "time-out!"); the third component (*bottom*) was a short text showing the participant how long it took him/her to solve the matrix, and a comparison to the aforementioned average performance (see Figure 1, bottom).

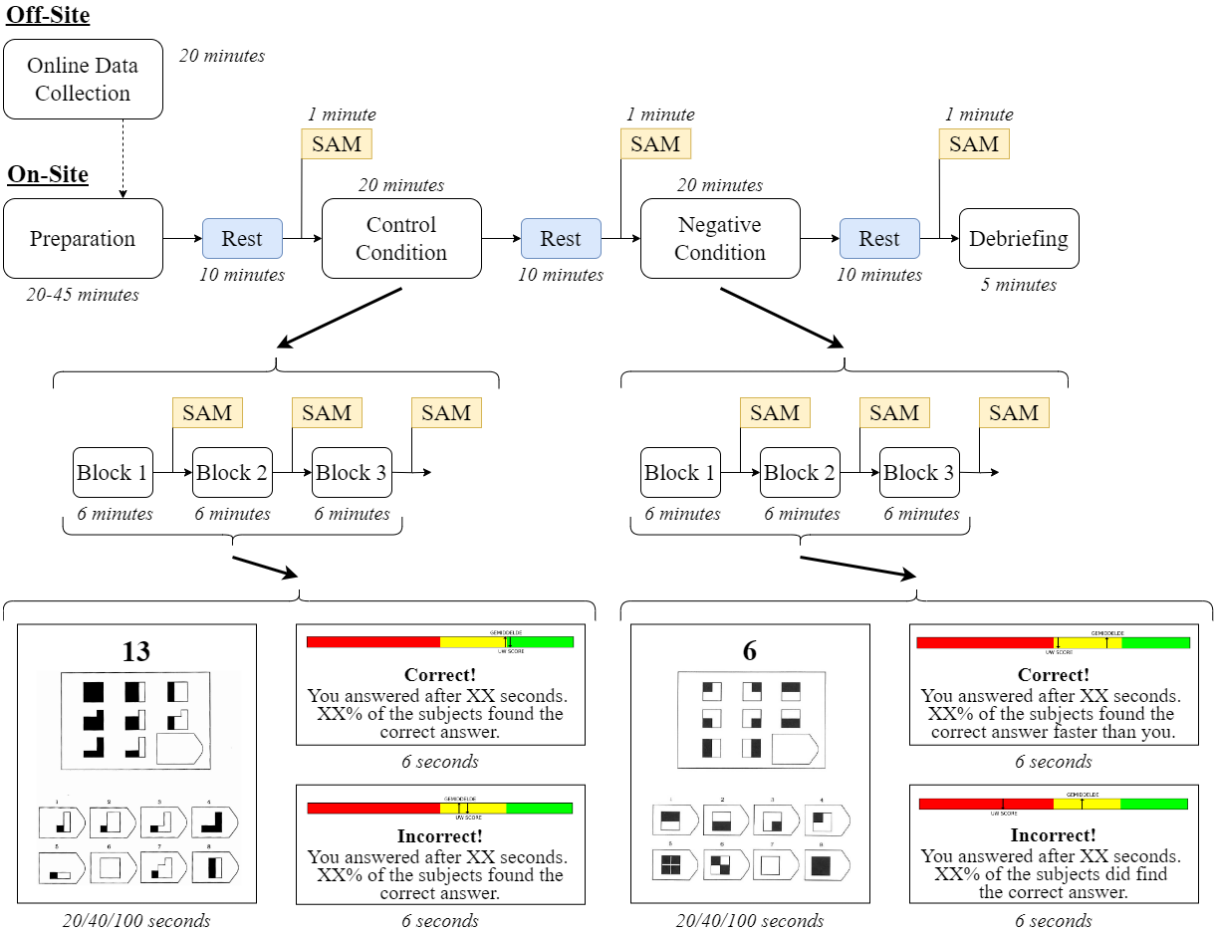

Figure 1: Visualization of the study paradigm. **Legend:** *Off-Site*: start of the study where a participant reads and signs the informed consent and afterwards completes the trait questionnaires. *On-Site:* part of the study where the participant comes to the University Hospital. *SAM*: moment when a self-assessment manikin questionnaire is recorded. *Preparation*: participant signs the informed consent again, EEG and other electrodes are applied. *Rest*: Resting-State, eyes closed EEG recording. *Control Condition*: participant performs the task, with neutral feedback. *Negative Condition*: participants performs the task, but receives negative feedback, regardless of their performance. *Debriefing*: end of the experiment. Participants are told about the goal of the study, are told that the feedback in the negative condition was not real, and are thanked for their participation. *Block 1/2/3*: block of a condition. Each block lasts either 6 minutes, or ends when a participant has solved all 11 Raven's Matrices assigned (randomly) to the specific block.

2.2.3. Cover story and manipulation

To induce psychosocial stress, participants were told that the study investigated possible EEG indices that might be indicative of future (either academic or professional) success in life. Participants were told that to investigate this, they would solve a well-known IQ test (i.e., Raven's matrices) while EEG data was collected. Participants were further told that to assess future success, their performance would be compared with two groups. Firstly, they would be compared with a control group of average individuals (i.e., the control condition) and afterward, they would be compared to individuals who achieved significant academic or professional success in their life (i.e., the negative condition). Finally, participants were told that their

performance was calculated based on both the correctness of their answers and the time it took to solve each trial.

The manipulation happened in the feedback that the participants received. During the control condition, regardless of the performance of the participant, the feedback showed that the individual performance was about equal to the average performance of the comparison group. This was shown in the comparison bar (top) and the short text (bottom), which declared what percentage of the subjects in the comparison group found the correct answer. During the negative condition, in each block participants' performance started roughly on par with the comparison group, but became progressively worse while the participant progressed through the block, regardless of the true performance of the participant (see section 7.6.2.). The progression from being on par to performing below the average was chosen to increase the believability of the feedback. This was shown in the comparison bar, which indicated that the personal score decreased while the average score remained similar throughout the exercises. The short sentence at the bottom also changed slightly, now indicating what percentage of people found the answer quicker than the participant when they answered correctly, or which amount of participants did find the correct answer when the participant answered incorrectly or did not give an answer in time (see Figure 1, bottom).

2.2.4. Self-assessment manikin

To assess the mental state of the participants throughout the experiment, the self-assessment manikin (SAM), a non-verbal questionnaire that assesses the state affective reaction of an individual, was conducted (Bradley & Lang, 1994; Lang, 1980). The SAM consists of two rows, each containing 9 pictures, indicating various levels of arousal and valence, and the participants selected a picture in each row that best corresponded to their emotional state at that moment. The picture scale corresponds to a Likert scale (range 1-9). The SAM was chosen, aside from its simple design and easy interpretation, to make it less likely that participants became aware of the goal of the study (i.e., repeated questions related to "stress" or "negative feelings" might make participants suspicious). The pictures as well as the corresponding instructions can be found in section 7.6.3.

2.3. ECG analysis

To assess whether negative feedback elicited a physiological reaction, the ECG data were analyzed during the feedback segments. Event-related cardiac responses, computed using inter-beat intervals (IBIs) which indicate the time between individual heartbeats, were therefore analyzed (Gunther Moor et al., 2010; van der Veen et al., 2014). To analyze the feedback moments, the R-peak closest to the onset of the feedback was selected and the IBI compared to the previous R-peak was computed and defined as IBI_0. From IBI_0, the three preceding IBIs (IBI_{-3}, IBI_{-2}, IBI_{-1}) and eight subsequent IBIs (IBI_1 until IBI_8) were also computed (see supplementary materials for more information, link: https://osf.io/yvzr5). All IBIs were then re-referenced to IBI_{-2}, thus obtaining IBI-difference scores (similar to previous research, see Gunther Moor et al., 2010; van der Veen et al., 2014). Positive/negative IBI-difference scores can be interpreted as a heart rate acceleration/deceleration (compared to the reference, IBI_{-2}).

2.4. EEG equipment and analysis

2.4.1. EEG equipment

EEG data was collected at 57 standard locations according to the international 10-10 system using a 64-channel, Ag/AgCl electrode Waveguard cap (ANT Neuro, the Netherlands) combined with a MICROMED SD LTM 64 EEG amplifier (Micromed S.p.A., Mogliano, Italy). Cz was used for online referencing while AFz was used as ground. Given the limited recording channels of the amplifier, four channels (PO7, PO8, O1, O2) were omitted from EEG recording for physiological data recording (electrocardiography (ECG) and electrodermal activity (EDA))). Electrode impedances were kept below 20 kΩ during data acquisition and data was collected at a sampling rate of 512 Hz. Data was filtered online using a high-pass filter at 0.008 Hz.

2.4.2. Preprocessing

EEG data were preprocessed using BrainVision Analyzer (Version 2.1., Brain Products GmbH, Gilching, Germany). Before preprocessing, the complete control and negative condition segments were extracted from the continuous EEG recording. The following preprocessing steps were performed for both EEG segments identically. Firstly, irrelevant channels for EEG preprocessing (i.e., ECG and EDA channels) were removed. Secondly, all data were filtered (50 Hz (Notch Filter), 1 - 40 Hz (IIR bandpass filter, 48 decibels/octave)). Thirdly, bad channels (channels with high amounts of electrical noise, identified by visual inspection) were

interpolated (topographic spline interpolation, spline order = 4, maximal degree of Legendre polynomials = 10, lambda = 1e-5). Fourthly, Independent Component Analysis (ICA) with standard settings was performed and components representing eye movements, heart rhythm activity, or muscle movement were manually selected (based on their topography and time course) and removed. Afterward, remaining artifacts were detected based on three criteria: gradient (maximum allowed voltage step of 50 μV/ms), min-max (maximum allowed voltage range of 200 μV/200 ms), and low activity (minimum of 0.5 μV/100 ms). Artifacts detected by this method were tagged 200 ms before and after the identified artifact. Epochs of 6.2 seconds were created based on the feedback triggers (200 ms before until 6 seconds (feedback exposure duration) after the trigger) and epochs containing artifacts were removed. Finally, the EEG data were re-referenced to an average reference, and data was exported in EDF+ format for further analysis. A visual representation of the preprocessing pipeline and the preprocessed data (not the raw data) can be found on OSF (link: https://osf.io/qxmgy).

2.4.3. Sensor level analysis

For the sensor level analysis (i.e., analysis of the time series measured by the electrodes) average power in the theta (4 - 8 Hz), alpha (8 - 13 Hz), and beta (13 - 30 Hz) frequency band of 6 frontal electrodes (F7, F3, Fz, FPz, F4, F8) was computed. Preprocessed EEG data were first converted from EDF+ format to MATLAB .mat files for further usage (these files can be found on OSF; link: https://osf.io/tywxp). Relative power, meaning the average power in a defined frequency band divided by the total power of the considered spectrum (1 - 40 Hz), was computed. Power of the EEG signals was computed using Welch's spectral power density estimate (MATLAB function: *pwelch*) and a 1/f noise correction is employed with the correction exponent equal to one (Cohen, 2014). Relative power was computed for each of the aforementioned electrodes separately and the average of these values is calculated to obtain a mean power estimate of the frontal cortical regions. All sensor level analyses were performed using custom code in MATLAB and can be found on OSF (link: https://osf.io/tywxp).

2.4.4. Source level analysis

2.4.4.1. Source modeling

EEG source modeling was performed using the Brainstorm Toolbox (Tadel et al., 2011). The USCBrain atlas and corresponding T1 weighted MRI image were used for this processing step as no individual MRI images of the participants were available (Joshi et al., 2022). The T1 image is an average image from five different high-resolution MRI scans from a single right-handed female. The EEG electrodes were co-registered to the MRI image using LPA, RPA, FPz, and Oz as landmarks and the obtained coordinates were converted to the corresponding MNI coordinates. To construct the head model, the SimNIBS *mri2mesh* Finite Element Method (FEM, known for its high spatial resolution; Cuffin et al., 2001) was employed, resulting in a 5-layer (scalp, skull, gray matter, white matter, and cerebrospinal fluid) FEM mesh of 642359 vertices (Thielscher et al., 2015; Windhoff et al., 2013). To solve the forward problem and obtain the leadfield matrix, evenly spaced (5 mm) dipoles were defined in the gray matter (15269 in total), and the placement of the electrodes was finalized by visual inspection using the aforementioned landmarks and projecting the electrodes directly on the scalp. The forward model and corresponding lead field matrix were obtained using the DUNEURO toolbox within Brainstorm (Medani et al., 2021). Isotropic conductivities were used (scalp = 0.43, skull = 0.008, GM = 0.33, WM = 0.14, CSF = 1.79) and the default options were used for the FEM solver type and source model. To solve the inverse problem, the orientation of the dipoles was constrained and set to be normal to the cortex and current density maps (unit Ampere-Meters) were obtained using the weighted minimum norm estimation method (wMNE, known for the limited spatial leakage; Song et al., 2015; Stenroos & Hauk, 2013) with default options for depth weighting and regularization. Sensor noise was estimated using the diagonal of the noise covariance matrix. Finally, time series of all scouts of the USCBrain atlas (65 regions in each hemisphere, 130 in total) were obtained by taking the mean of all dipole values belonging to a scout. The obtained scout time series were extracted from the Brainstorm toolbox for subsequent analyses. The standard settings for the different steps can be found in the supplemental materials (section 7.6.5.1.).

2.4.4.2. Mapping of brain regions to atlas regions

As indicated in the introduction, various brain regions of interest (ROIs) have been identified in previous research (Berretz et al., 2021; Cacioppo et al., 2013; Dedovic et al., 2009; Kogler et al., 2015; van Oort et al., 2017; Wang et al., 2017). Based on the literature, we selected 10 regions (five regions in each hemisphere) for further investigation: the *anterior insula*

(combined with parts of the pars triangularis and opercularis), the *ACC*, the *PCC*, the *precuneus,* and the *orbitofrontal cortex*. Table 1 shows which regions (called scouts) of the USCBrain atlas have been selected for further analysis. Given the limited temporal resolution of EEG, multiple USCBrain scouts were combined for the anterior insula and orbitofrontal cortex to obtain brain regions that are within the spatial resolution possibilities of EEG. If multiple regions of the atlas were selected, a single time series was obtained by extracting the first principal component of the selected time series using principal component analysis. The selected brain ROIs are shown in Figure 2.

Table 1: Conversion of brain ROIs to scouts of the USCBrain Atlas (Joshi et al., 2020).

Brain ROI	**USCBrain Scouts (L)**	**USCBrain Scouts (R)**
Anterior Insula	Insula – anterior L	Insula – anterior R
	Pars Opercularis – Inferior L	Pars Opercularis – Inferior R
	Pars Opercularis – Superior L	Pars Opercularis – Superior R
	Pars Triangularis – Middle L	Pars Triangularis – Middle R
	Pars Triangularis – Posterior L	Pars Triangularis – Posterior R
PCC	Cingulate Gyrus – Posterior L	Cingulate Gyrus – Posterior R
Precuneus	Precuneus – Inferior L	Precuneus – Inferior R
ACC	Cingulate Gyrus – Anterior L	Cingulate Gyrus – Anterior R
Orbitofrontal Cortex	Anterior Orbito-frontal Gyrus L	Anterior Orbito-frontal Gyrus R
	Gyrus Rectus L	Gyrus Rectus R
	Middle Orbito-frontal Gyrus L	Middle Orbito-frontal Gyrus R

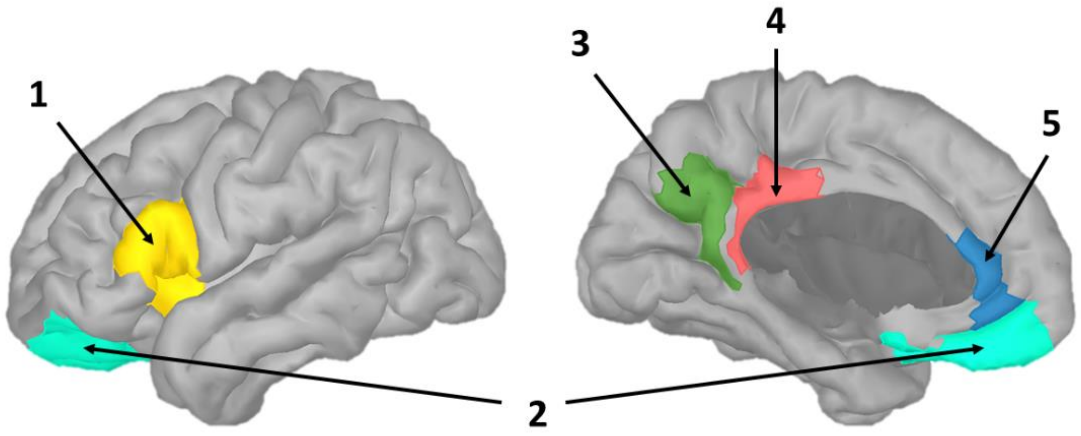

Figure 2: Visualization of the investigated brain ROIs. **(1)**: Anterior Insula; **(2)**: Orbitofrontal Cortex; **(3)**: Precuneus; **(4)**: Posterior Cingulate Cortex (PCC); **(5)**: Anterior Cingulate Cortex (ACC).

Note: Only the left hemisphere is shown in this figure, the contralateral ROIs are also included in the analyses.

2.4.4.3. Power analysis

Power analysis on source level was conducted identically as on sensor level (see section 2.5.3.). Relative power of the theta (4 - 8 Hz), alpha (8 - 13 Hz), and beta (13 - 30 Hz) frequency range was computed for the brain regions defined in Table 1. All source level power analyses were performed using custom code in MATLAB. The analysis scripts can be found on OSF (link: https://osf.io/tywxp).

2.4.4.4. Functional connectivity analysis

To assess functional connections between the brain ROIs (see Table 1), amplitude envelope correlation (AEC), a robust linear, undirected, and bivariate FC measure was used (Brookes et al., 2011, 2012; Colclough et al., 2016; Hipp et al., 2012). To calculate AEC, the time series of each brain region were band-passed so only the signals in a specific frequency range were considered (see Figure 3.1.). The band-passed signals were then pairwise orthogonalized (see Figure 3.2.) using a stabilized Gram-Schmidt orthogonalization algorithm. Orthogonalization was performed to minimize the effect of spatial leakage due to the blurring effect of the weighted minimum norm estimation, which could lead to spurious functional connections (Nunez & Srinivasan, 2006). Since this orthogonalization method is non-symmetric (i.e., GSO(Sig_1, Sig_2) does not equal GSO(Sig_2, Sig_1)), orthogonalization was performed twice and all steps described below were conducted on each pair of orthogonalized signals. The final FC value was obtained by averaging the two FC values. Next, the power envelope of the orthogonalized time series was obtained by applying a Hilbert transform (MATLAB function: *hilbert*) and subsequently taking the absolute value of the Hilbert-transformed signal (see Figure 3.3.). Finally, the correlation between both power envelopes was calculated, resulting in a single AEC value that describes the functional connectivity strength between two brain regions (see Figure 3.4.). This analysis was conducted for each epoch and frequency band separately, and the final AEC value was obtained by averaging the epoch-specific AEC values.

Due to the large amount of possible functional connections which can be computed (for 10 brain regions and 3 frequency bands; 135 connections), initial results of the source power analysis were used to reduce the search space for the FC analysis. These initial results showed changes in activity within the alpha and beta frequency range and showed that the left and right precuneus seemed to be highly affected. Therefore only connections between the left or right precuneus and the other regions in the alpha and beta frequency range were considered. This led to 34 (17 connections, 2 frequency bands) possible connections. All source level functional

connectivity analyses were performed using custom code in MATLAB. The scripts can be found on OSF (link: https://osf.io/tywxp).

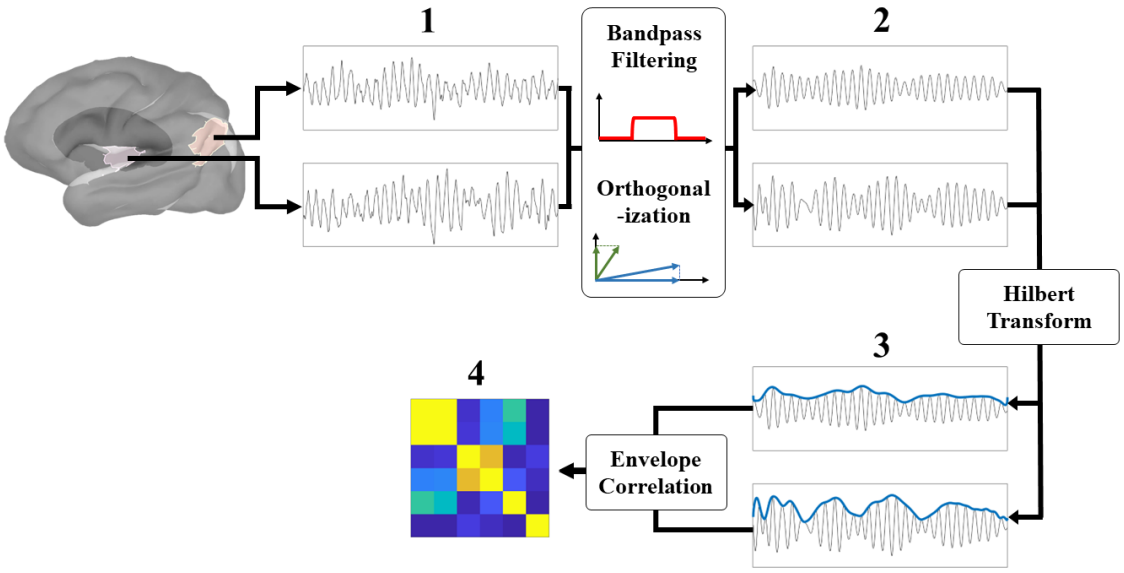

Figure 3: Visualization of the functional connectivity analysis. **(1)**: Selection of the timeseries of brain ROIs of interest. **(2)**: Preparing the timeseries by bandpass filtering (to only investigate the frequency band of interest) and orthogonalization (to eliminate spatial leakage due to the blurring of the minimum norm estimation). **(3)**: Computing the amplitude envelope of each timeseries using the Hilbert transform. **(4)**: Computing the correlation between the timeseries to obtain the AEC value.

Note: The orthogonalization step is performed twice, as are all subsequent steps for each set of orthogonalized timeseries.

2.5. Statistical analysis

Statistical analysis was conducted using R (version 4.1.1.) and RStudio (version 2022.02.1.). All information regarding the statistical analysis can be found on OSF (the script: https://osf.io/u8zyv; information regarding used packages: https://osf.io/ekfcp; how to run the analysis: https://osf.io/vgz3x; how to convert EEG results to statistical tables: https://osf.io/389r4; the script of the Bayesian analysis : https://osf.io/76jev).

2.5.1. SAM analysis

For the SAM analysis (and all subsequent analyses), generalized linear mixed models (GLMMs) were employed (R package: *lme4*). The score on each scale (valence, arousal) was defined as a dependent variable, while the condition (control, negative) was used as a fixed effect and participant ID as a random effect (R formula: *Scale_score ~ Condition +*

(1|Participant_ID)). Two models were trained: a linear mixed model (LMM) and a generalized linear mixed model (GLMM) using a gamma distribution and identity link. The models were compared using the Akaike Information Criterion (AIC), which assesses how much variance in the data is explained by the model (i.e., a lower AIC score indicates more variance is explained), and the model with the lowest AIC score was selected. The possible added value of participants' sex was assessed by building a new model with sex included as a fixed effect (R formula: *Scale_Score ~ Condition + Sex + (1|Participant_ID)*) and comparing both models using an ANOVA test (type III). Given the preference for parsimonious models (i.e., models with fewer fixed or random effects are easier to interpret, and are less likely to overfit; Bates et al., 2018), if the ANOVA showed that the model with sex as effect did not explain the variance in the data significantly better (i.e., the *p-value* of the ANOVA test is > 0.05) it was concluded that the sex of the participants did not contribute significantly and was therefore excluded from the model. See Kappen et al., (2022) for a detailed explanation.

2.5.2. ECG analysis

Analysis of the ECG-IBI data was similar to the SAM analysis. The twelve IBI-differences (IBI_{-3} to IBI_{12}) were the dependent variable, condition (positive, negative) a fixed effect, and participant ID a random effect (R formula: *IBI-difference ~ Condition + (1|Participant_ID)*). The possible added value of sex was assessed identically as the SAM analysis (see section 2.5.1.). Contrary to the SAM analysis, however, only a linear model was computed due to the presence of negative values for the dependent variable, which is incompatible with gamma distributions. See Kappen et al., (2022) for further explanations.

2.5.3. EEG power analysis

Before the statistical analysis of the EEG measures was performed, participants who did not have at least 15 epochs for both conditions (i.e., the neutral and negative feedback condition) were not included in the analysis, which lead to the exclusion of three participants. A full overview of the epoch amount for each participant can be found on OSF (link: https://osf.io/49azx).

2.5.3.1. Frequentist statistical analysis

For both the sensor and source power analyses, a similar approach as the SAM and ECG analysis was employed. The power values of either the mean of the frontal electrodes or the individual brain regions were the dependent variable, while the condition was a fixed effect and the participant ID a random effect (R formula: *PowerValue ~ Condition + (1|Participant)*).

Both an LMM and GLMM were trained, given the fixed range of power values ([0, 1]; 0 = no power; 1 = all power) and model selection was performed using AIC (see section 2.5.1.). The possible added value of sex was assessed identically as in section 2.5.1. Estimated marginal means (EMMs) were computed (using the *emmeans* function), and the *p*-value from the *Condition* contrast was obtained. To gain further insight into the results, standardized effect sizes (SES, similar to Cohen's D but adapted for non-normal disributions) and corresponding confidence intervals (CI) were computed (*eff_size* function).

2.5.3.2. Bayesian statistical analysis

For the sensor power analyses, a subsequent Bayesian analysis was conducted, as we hypothesized the absence of a significant difference between conditions. Firstly, two GLMMs with gamma distributions were trained for the power values of each frequency band separately. The first model was identical to the model described in the previous section, with the power value as dependent variable, the condition and participant sex as fixed effect and the participant ID as random effect (R formula : *PowerValue ~ Condition + Sex + (1|Participant)*). The second model (the null model) was trained without the condition as fixed effect (R formula : *PowerValue ~ Sex + (1|Participant)*). The Bayes factor (BF01) comparing both models was computed using the formula by Wagenmakers, which employs the Bayes Information Criterion (BIC) and does not require the definition of prior distributions (Wagenmakers, 2007). BF01 compares the likelihood of the data under the null model, which did not include *condition* as a fixed effect (H_0) with the likelihood of the data under the alternative model, which includes *condition* as fixed effect (H_A). Larger BF01 values suggest the presence of evidence that favors the null hypothesis (H_0) and the obtained BF01 factors were interpreted according to Jeffreys (Jeffreys, 1961).

2.5.4. EEG functional connectivity analysis

For FC values, statistical analyses were conducted similarly to section 4.5.3. The main difference is that, since AEC has a range of [-1, 1], gamma GLMMs are not always possible given the inability of gamma GLMMs to work with non-positive values. Therefore, LMMs are always trained, and if possible (i.e., the currently considered functional connection does not have negative values for any participant) gamma GLMMs were trained. The further analysis was conducted as described in section 2.5.3.

2.5.5. Multiple comparison correction

To correct for the multiple tests that were conducted (67; 3 (sensor level power), 30 (10 x 3 source level power), 34 (17 x 2 source level FC)), all obtained p-values were corrected for multiple comparisons using the false discovery rate correction method (FDR; Benjamini & Hochberg, 1995). These FDR-corrected p-values are reported in the result section.

3. Results

Given that this article is part of a larger project, the SAM and ECG analysis (sections 2.2.4. and 2.3.) have also been described in another article (Kappen et al., 2022). We refer the interested reader to the aforementioned article by Kappen and colleagues (2022) for further information.

3.1. SAM results

The GLMMs with gamma distributions (one for each axis of the SAM; R formula = *Scale_score ~ Condition + (1|Participant_ID)*) revealed a significant C*ondition* effect for both valence and arousal. Valence decreased significantly during the negative condition compared to the control condition ($p < 0.001$), confirming our hypothesis (Kuppens et al., 2013). Arousal also decreased significantly between the control condition and negative condition ($p = 0.034$), contradicting our hypothesis (Kuppens et al., 2013). See section 7.6.3. for a visualization of the results.

3.2. ECG results

A Generalized Linear Mixed Model (GLMM) with gama distribution (R formula = *IBI-difference ~ Condition + (1|Participant_ID)*) revealed a significant interaction effect for *IBI-difference x Condition*. During the negative feedback, IBI_2 to IBI_7 (with IBI_0 being the one closest to the feedback onset) were significantly lower than during the control feedback (p's <= 0.001), thus indicating that negative feedback resulted in an increased heart rate acceleration, confirming our hypothesis that negative feedback would result in an increase in sympathetic reactivity (see section 7.6.4. for a visualization of the results).

3.3. EEG results

A summary of all EEG results (regardless of significance) can be found in section 7.6.5.2. In the following sections, only significant results will be described.

3.3.1. Sensor level

The frequentist statistical analysis from GLMMs with gamma distributions (R formula = *PowerValue ~ Condition + (1|Participant)*) indicated that no significant changes for the sensor level analyses (frontal theta, alpha and beta power) were found (*p*'s > 0.16). The subsequent Bayesian statistical analysis provided moderate evidence in favor of the null hypothesis for theta power (BF01 = 6.40) and beta power (BF01 = 8.79). For alpha power, the Bayesian analysis provided anecdotal evidence in favor of the null hypothesis (BF01 = 1.24).

3.3.2. Source level

Five source level results are significant, all significant results are from GLMMs with gamma distributions (R formula = *PowerValue ~ Condition + (1|Participant)* for relative power measures ; R formula = *FCValue ~ Condition + (1|Participant)* for functional connectivity (FC) measures). The relative alpha power of the right posterior cingulate cortex (β = 0.018; *SE* = 0.0042; *t* = 4.202; *p* < 0.001; *standardized effect size (SES)* = 0.1 with *95% confidence interval (CI)* = 0.05; 0.15), left precuneus (β = 0.013; *SE* = 0.004; *t* = 3.124; *p* = 0.03; *SES* = 0.07; *CI* = 0.03;0.12) and right precuneus (β = 0.02; *SE* = 0.004; *t* = 4.385; *p* < 0.001; *SES* = 0.11, *CI* = 0.06; 0.16) all increase significantly in the negative- compared to the control condition, confirming our hypothesis. The functional connection in the alpha frequency range between the left- and right precuneus (β = 0.017; *SE* = 0.002; *t* = 8.188; *p* < 0.001; *SES* = 0.08; CI = 0.06; 0.1)) also increased in the negative condition. One further functional connection (between the right PCC and right precuneus in the beta frequency range) remained significant after multiple comparison correction, but the model failed to converge due to the minimal difference between conditions, and thus will not be discussed further. All other analyses revealed no significant differences between conditions (*p*'s > 0.15), contradicting our other hypotheses regarding an increase in beta power in the anterior insulae (Berretz et al., 2021). For all models, sex did not improve the models significantly (all *p*'s > 0.12).

4. Discussion and conclusion

Previous research investigating the neural signature of the psychosocial stress response through means of EEG has identified changes in several EEG indices, most notably band power (Vanhollebeke et al., 2022). A recent article by Ehrhardt and colleagues (2021), however, has shown that two of the most commonly investigated indices, frontal alpha, and beta power, do not seem sensitive enough to change significantly by psychosocial stressors alone. Previously reported alfa and beta band power changes might therefore not reflect the influence of psychosocial stressors themselves, but rather the influence of co-occurring stressors such as time pressure or cognitive processes related to the task at hand. While this insight is puzzling and demands reflection within the research field, it is possible that other EEG indices, such as source level-derived power and functional connectivity measures, do change significantly due to psychosocial stressors alone. To investigate this, we exposed a large sample of healthy adults to a psychosocial stressor using a within-subjects design by providing manipulated feedback. Participants were shown either a personal performance on par with a comparison group (*control* condition) or a worse personal performance compared to a group of high-achieving peers (*negative* condition). We kept other stressors such as time limits or cognitive tasks constant in both conditions and to further exclude cognitive processing-related oscillatory interferences, we only analyzed the EEG data collected during feedback exposure. Aside from EEG data, we also collected ECG data to investigate whether psychosocial stressors lead to a short-term physiological reaction and a state questionnaire, the self-assessment manikin, to probe the mental state of the participants.

Analysis of the IBIs from the ECG data during the feedback revealed that during the negative condition, the IBI-difference from IBI_2 to IBI_7 was significantly shorter than during the control condition, indicating a higher heart rate acceleration during the negative condition (Kappen et al., 2022). Heart rate acceleration is a sign of sympathetic nervous (re)activity, which is known to be increased due to stress (Taelman et al., 2009; Vrijkotte et al., 2000; Ziegler, 2012). The higher heart rate acceleration during the negative condition, therefore, indicates a higher short-term sympathetic reactivity, indicating the effect of the psychosocial stressor. Results of the SAM showed a significant decrease in both valence and arousal. The decrease in valence aligns with our hypothesis and indicates the effect of the negative feedback on the mood of the participants. The decrease in arousal does not align with our hypothesis, and might reflect a possible order effect due to the control condition being before the negative condition or an unclear translation of the word *arousal* to Dutch (which has the same translation of the English

word *excitement*). Given the increased heart rate acceleration and decrease in valence in the negative condition however, we conclude that the psychosocial stress induction was successfull.

Analysis of the EEG data shows that on the sensor level, frequentist statistical analysis revealed no significant changes in either theta, alpha, or beta power of frontal electrodes between conditions. These results reaffirm the results of Ehrhardt and colleagues (2021) and show that, when employing frequentist statistics, psychosocial stressors alone are not capable of inducing significant changes in these commonly employed sensor level EEG measures. The subsequent Bayesian analyses further provided moderate evidence in favor of the null hypothesis (i.e., psychosocial stressors do not lead to significant changes in sensor level band power of frontal electrodes) for theta and beta power. For theta power, the BF01 was 6.4, suggesting that our results are 6.4 times more likely to be observed under the null hypothesis. Our recent systematic review found contradicting results regarding theta power, which might be explained by the fact that this EEG measure is not sensitive enough to detect psychosocial stress related neuronal changes, as our results suggest (Vanhollebeke et al., 2022). Similarly, the BF01 for beta power was 8.79, suggesting that the null hypothesis is 8.79 more likely given our results. This result is also in line with our recent meta-analysis, which revealed a non-significant effect size for beta power across studies (Vanhollebeke et al., 2022). Contrary to the Bayes factors for theta and beta power, only anecdotal evidence in favor of the null hypothesis for alpha power was found (BF01 being 1.24). Our meta-analysis for alpha power identified a significant effect size, and alpha power was found to be the best feature for mental stress detection in another recent review (Katmah et al., 2021; Vanhollebeke et al., 2022). Although our results regarding alpha power at frontal electrodes align with those of Ehrhardt and colleagues (2021), no strong evidence was found for the null hypothesis either. Future studies should therefore further examine the exact influence of psychosocial stressors on frontal alpha power changes. While the weight of this conclusion cannot be ignored, it should be noted that in both the article of Ehrhardt and colleagues (2021) and the current article, subtle psychosocial stressors are employed. Ehrhardt and colleagues (2021) used a video camera and the announcement of the analysis of performance and behavior while in the current article manipulated feedback was employed as a psychosocial stressor. It is possible that more potent psychosocial stressors, such as direct exposure to an unfriendly panel of experts in the TSST (Kirschbaum et al., 1993), are capable of inducing sensor level EEG changes (for an overview of articles that use the TSST with EEG, see the supplementary materials of Vanhollebeke et al., 2022). Further is it also possible that band power changes in other electrodes, aside from those

investigated in the current article, are sensitive to psychosocial stressor induced neural changes. An exploratory whole-brain, sensor-level analysis for theta, alpha, and beta power was conducted (link: https://osf.io/epk8c) that indicated no significant changes in the theta and beta range (theta power results: https://osf.io/zepu4; beta power results: https://osf.io/dq27w), but showed that alpha power changed significantly between the neutral and negative feedback condition for several parietal electrodes (link: https://osf.io/pkejw). These significant changes might reflect the observed effect in the precuneus and PCC and demonstrate the value of assessing psychosocial stress at electrodes outside of the commonly investigated frontal electrodes (Vanhollebeke et al., 2022). Regardless, technical problems in sensor level analyses related to volume conduction, whereby activity of (mainly) occipital neural generators are picked up by frontal electrodes, should be considered and sensor level power measures therefore, need to be interpreted with severe caution (Schaworonkow & Nikulin, 2022).

In the source space, in contrast to the non-significant results of the commonly employed sensor level EEG indices, a significant increase in alpha power in the right precuneus and posterior cingulate cortex (PCC), as well as the left precuneus, are found in the negative, compared to the control condition. Furthermore, an increase in functional connectivity between the left and right precuneus, computed using amplitude envelope correlation, was observed. The significant changes found in source space all point to a single direction: an increase of activity and connectivity in the alpha band of the precuneus/PCC complex. Oscillations in the alpha frequency range are assumed to reflect an inhibitory coordination system within the brain (Jensen & Mazaheri, 2010; Mathewson et al., 2011) and increases in alpha power are therefore expected to reflect decreases in cortical activity (Allen et al., 2004). Our results thus implicate that a short-term psychosocial stressor leads to an acute decrease in cortical activity of the precuneus/PCC cluster. This decrease in precuneus/PCC activity aligns with a recent meta-analysis of fMRI studies studying psychosocial stress, which also found a decrease in (BOLD) activity in the precuneus and PCC (Berretz et al., 2021). Interestingly, studies investigating trial-based manipulation-free social comparisons also report changes in precuneus and PCC activity (Fliessbach et al., 2007; Lindner et al., 2015). These studies, however, sometimes find increased precuneus/PCC activity, an incongruence also identified in another review of fMRI studies employing a variety of stressors (van Oort et al., 2017). This incongruence mainly highlights the complex interactions within the brain and indicates the necessity for further investigation. Finally, precuneus/PCC activity is also found in an EEG study investigating social comparisons (Sánchez-García et al., 2021). This study, which employed event-related potentials (ERPs) to

investigate social comparisons, identified the (pre)cuneus as the generator of an ERP (early negativity) when participants felt shameful in a social context, linking the cluster again to negative social comparison (Sánchez-García et al., 2021). Taken together, our results show that uncontrollable negative peer comparison leads to decreased activity of the precuneus/PCC complex.

The precuneus/PCC complex is a key region of the default mode network (DMN), a network active when no external tasks are presented to an individual which has been linked with self-reflective, internally directed thoughts (Fransson & Marrelec, 2008). Several studies have also identified increased activity in the precuneus/PCC complex during tasks related to self-reflection (Buckner & Carroll, 2007; Johnson et al., 2002; Lou et al., 2004). These activations can be explained by the integrative model of the PCC from Cavanna and colleagues, which poses that PCC activity increases when thoughts are more internally focussed (Cavanna & Trimble, 2006). Consequently, decreased activity of the precuneus and PCC have also been linked with tasks that are less self-oriented when compared to more self-oriented tasks (Lou et al., 2004). Activity changes in the precuneus and PCC have further been reported during emotion regulation. In a recent article of Guendelman and colleagues (2022), it was shown that increased activity of the precuneus/PCC (contrary to our findings of decreased activity) was associated with both lower self-reported stress as well as decreased autonomic sympathetic activation during emotion regulation (Guendelman et al., 2022). Increased precuneus activity has also been reported in women with higher self-compassion, and was further linked with decreased levels of perceived stress during the viewing of high arousal negative valence pictures (Pires et al., 2018). Disrupted precuneus/PCC activity is further identified in several stress-related psychiatric disorders, such as post-traumatic stress disorder (Andrewes & Jenkins, 2019), social anxiety disorder (Yuan et al., 2018), and depression (Grimm et al., 2009). Taken together, our results of decreased precuneus/PCC activity might thus imply a short-term attentional shift from internal towards external focus for the regulation of an acute external threat (i.e., a psychosocial stressor) (Cabanis et al., 2013; Cavanna & Trimble, 2006; Leech & Sharp, 2014).

While our results are promising and show that psychosocial stressors do lead to significant changes in EEG indices, it should be noted that these observed changes are small. The likely reason for the small effect sizes is the subtlety of the employed stressor and inherently limited sensitivity of EEG as a neuroimaging technique (Cohen, 2014). In conclusion, in this article, we have shown that source level-derived EEG indices are, contrary

to the commonly utilized sensor level-derived indices alpha and beta power of frontal electrodes, sensitive enough to investigate neuronal changes due to purely psychosocial stressors. The modest effect sizes hint at the limited capability of EEG to capture subtle mental changes in an individual. We therefore advise other researchers in the field to 1) use large participant groups; 2) employ within-subject designs and 3) use potent psychosocial stressors such as the TSST to further investigate the effects of pure psychosocial stressors on neural activity, as measured by EEG.

5. Limitations

Some limitations in the current study can be noted. Firstly, the possibility of an order effect due to the positioning of the conditions is present. This positioning was chosen since counterbalancing would only have been possible when the resting time between conditions would be multiple hours (or days), given the long recovery phase of stressors (Vaisvaser et al., 2013). However, as our results are in line with previous neuroimaging research (both fMRI and EEG), we believe that if present, order effects will have a minimal influence on our results. Secondly, the psychosocial stressor that was employed is subtle, which likely reduces the effect sizes. This makes it difficult to generalize our findings to all psychosocial stressors. Thirdly, the feedback screen consisted of multiple parts, so it might be possible that some confounding effects are introduced. Fourthly, the amount of EEG electrodes is relatively low for EEG source imaging. Related to this, a template MRI image is also used, which does not perfectly match the brain structure of the participants. The sizes of the chosen source level brain regions however are quite large, which makes the misattribution of electrical activity to regions not likely. Finally, it should be mentioned that aside from the brain regions investigated in this study, other regions, mainly subcortical regions not accessible by EEG due to their deep location within the brain, are also consistently reported in previous studies. It is likely that, to better understand the reaction of the brain to psychosocial stressors, these regions should also be considered.

6. References

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7. Supplemental information

7.1. Alterations from the published article

The final text above has some slight alterations from the published article in *Scientific Reports*. None of the alterations are related to the substance, but are done for the presentation of the article in its current form. These alterations are:

- Figure 1 : font change, enlargment of words, and color version.
- Table 1 : font change.
- Figure 3 : font change and enlargment of words.
- Text : the published article presented the results and discussion first, in this version materials and methods are placed first. Additionally supplementary materials are mentioned throughout the article, some have been listed below so instead these sections are mentioned now.
- References : the published articles used a different reference style (*Nature*), in this version the APA reference style is used.

7.2. Acknowledgments

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7.4. Declaration of competing interest

All authors report no financial interest or potential conflict of interest related to this publication

7.5. Open practices statement

All data, except for the raw EEG data, is available on OSF (link: https://osf.io/5qew6/). Code is available on OSF (link: https://osf.io/5qew6) and Github (link: https://github.com/dx2r/PhD_EEG_ Pipeline).

7.6. Supplementary materials

7.6.1. In- and exclusion criteria

- Non-Dutch speakers
- Left handed
- Born before 1970
- Psychology student
- Personal of family history of epilepsy
- Recent neurosurgical procedures
- Pacemaker or other electronic implants
- Inner ear prosthesis
- Metal or magnetic objects in the brain or around the head (removable earrings and piercings allowed)
- Pregnancy
- Unstable medical condition
- Current depressive episode
- Psychiatric disorder
- Skin disorder at the level of the head
- Current addiction (other than smoking)
- Current substance abuse
- Current use of psychotropic medication
- Eye disease (not solved by glasses)
- Heart, respiratory, or neurological problems
- Consumption of caffeine or nicotine less than 2 hours before the start of the experiment
- Dreadlocks

7.6.2. Supplemental figure 2

This figure was not included in the original article, and is adapted from the article by Kappen and colleagues (2022). Given that they report on the same data, the results are identical.

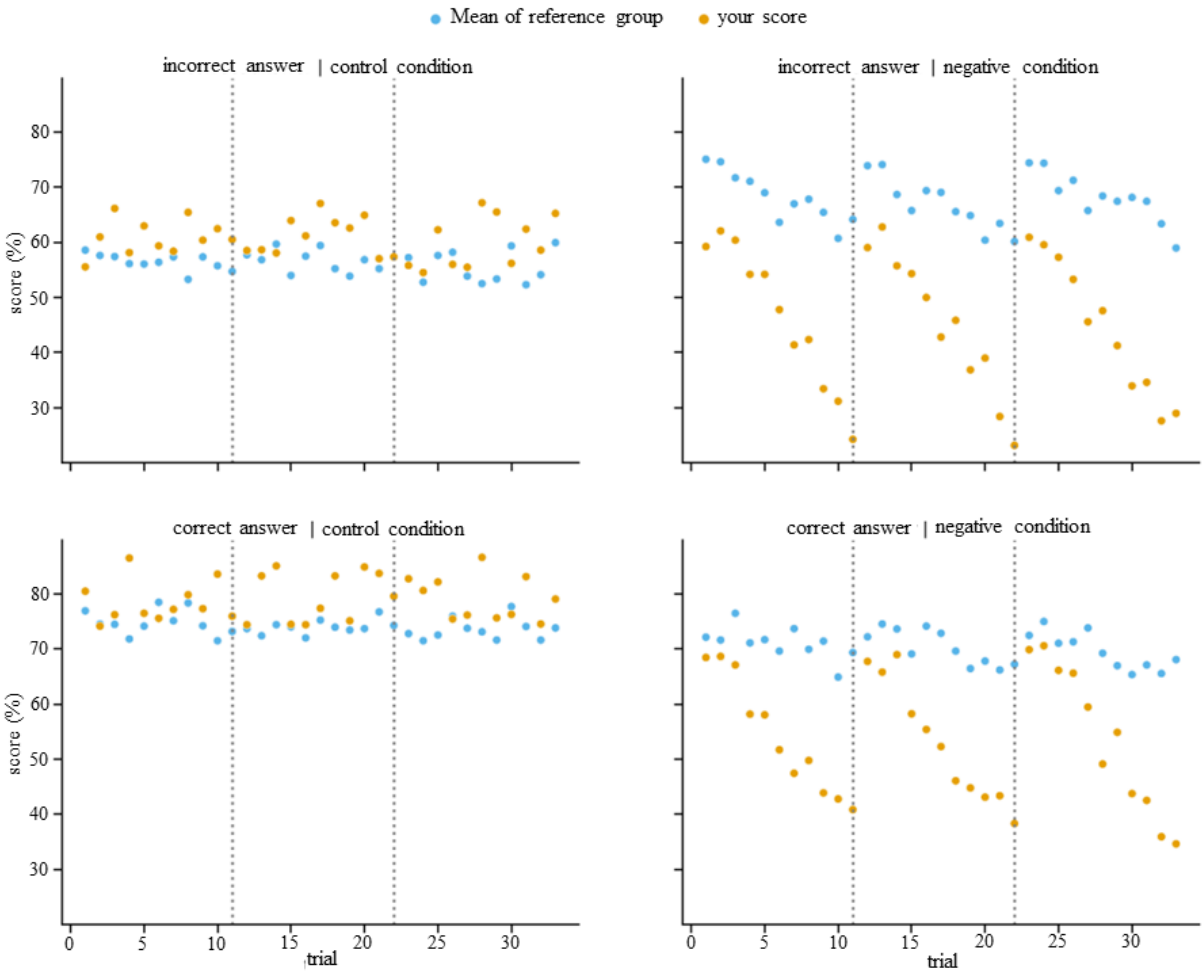


Figure (extra): Performance feedback as lines in the colored feedback bar. Blue dots stand for 'group performance', and orange dots stand for 'your performance'. Y-axis shows time over the condition (left two plots are control condition; right two plots are negative condition). Vertical dashed lines show separations for the subblocks (where a response block was executed).

7.6.3. Self-assessment manikin

7.6.3.1. Arousal scale

Question: ‘Duid aan welke manikin je huidige gevoelens het best representeert’

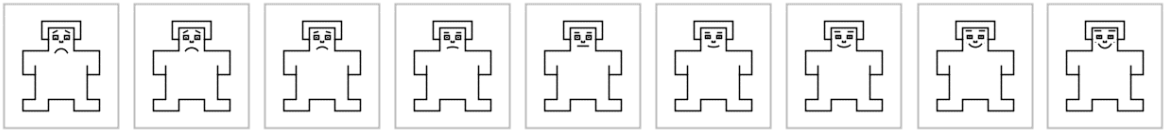
(*English : ‘Indicate which manikin best represents your current feelings’*)

Rustig (*Calm)* Opgewonden (*Excited)*

7.6.3.2. Valence scale

Question: ‘Duid aan welke manikin je huidige gevoelens het best representeert’

(*English : ‘Indicate which manikin best represents your current feelings’*)



Ongelukkig (U*nhappy*) Gelukkig (*Happy*)

7.6.3.3. Result figures

These figures were not included in the original article, and are adapted from the article by Kappen and colleagues (2022). Given that they report on the same data, the results are identical.

7.6.3.3.1. Arousal scale

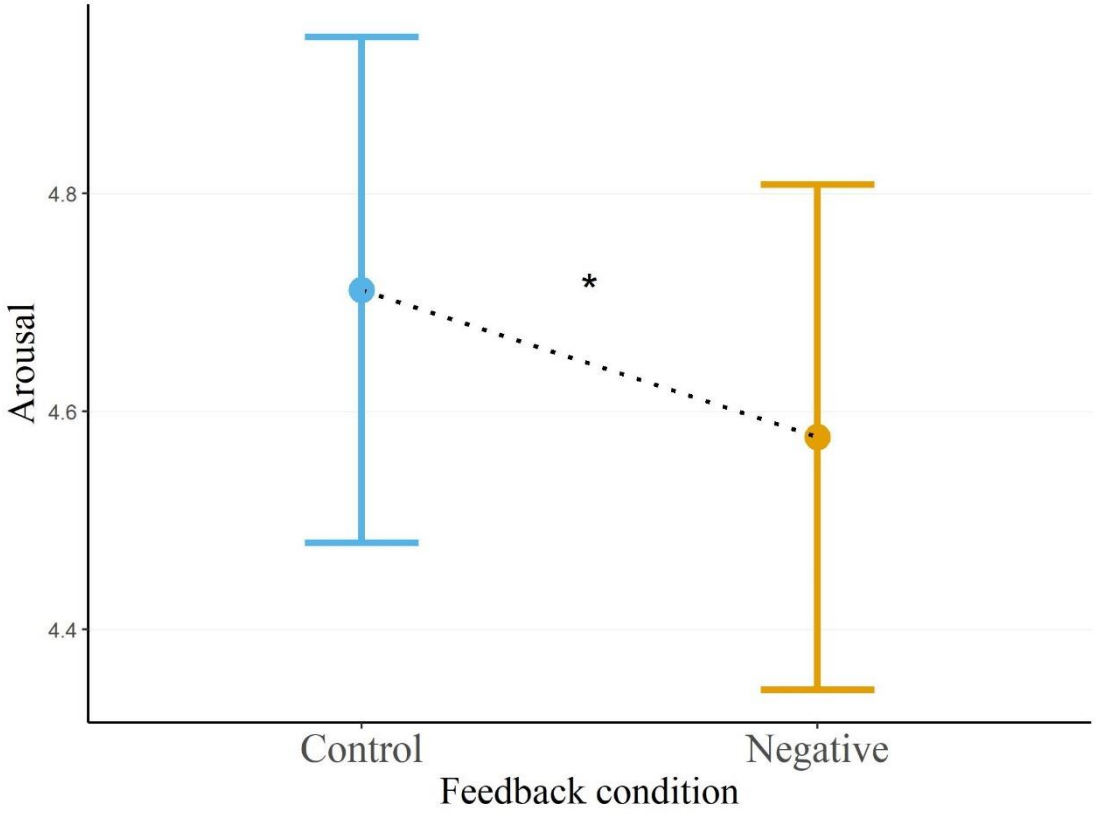


Figure (extra): Estimated marginal means (EMMs) of self-reported arousal during control-, and negative feedback condition after controlling for sex. Error bars depict standard error of the means (SEMs), asterisks indicate significance levels. * = $p < 0.05$.

7.6.3.3.2. Valence scale

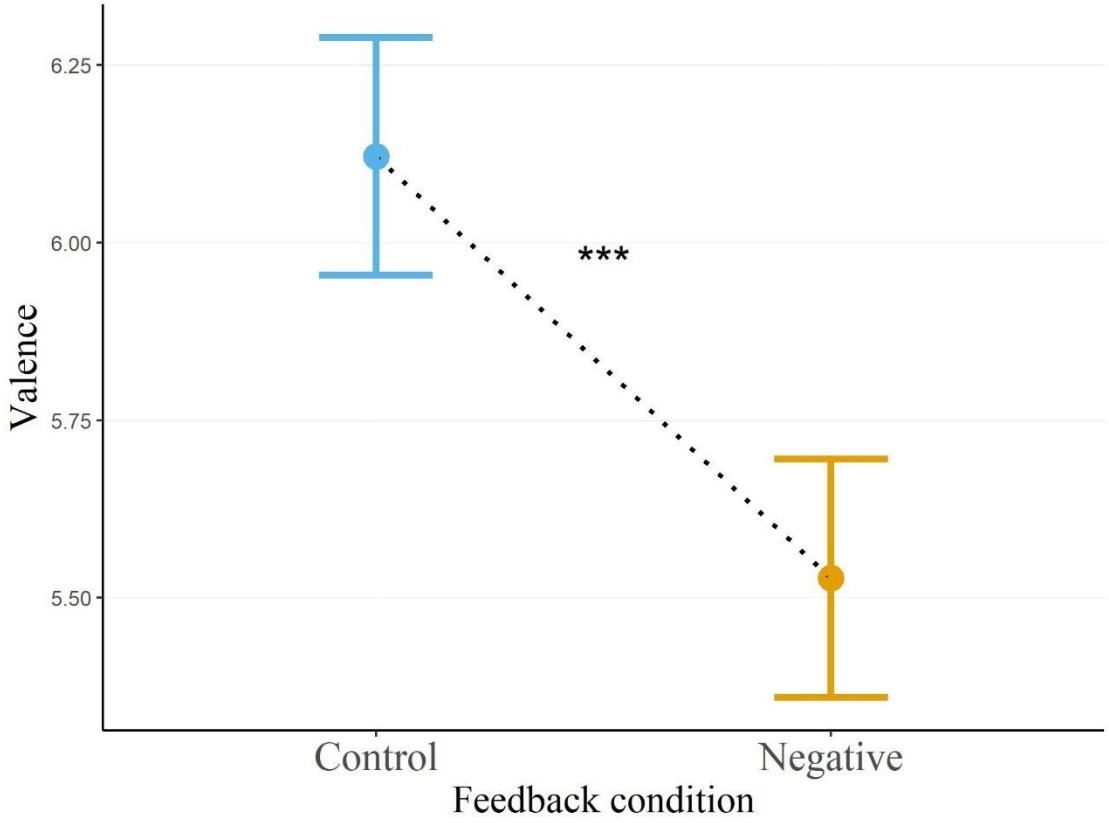


Figure (extra): Estimated marginal means (EMMs) of self-reported valence during control-, and negative feedback condition after controlling for sex. Error bars depict standard error of the means (SEMs), asterisks indicate significance levels. *** = $p < 0.001$.

7.6.4. ECG analysis

This figure was not included in the original article, and is adapted from the article by Kappen and colleagues (2022). Given that they report on the same data, the results are identical.

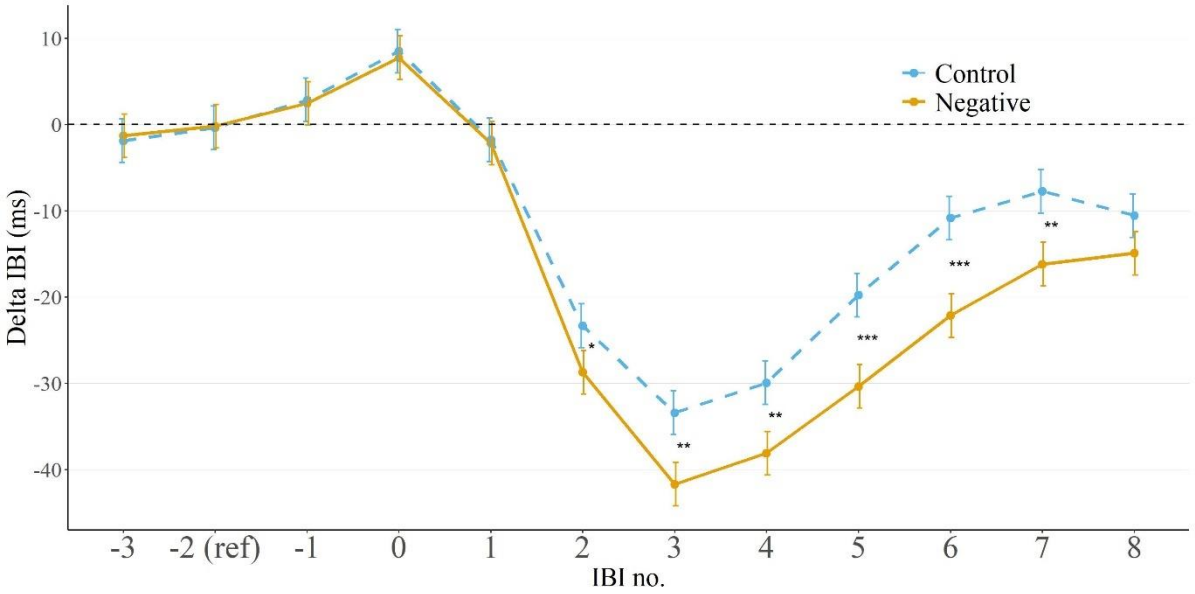


Figure (extra): Delta Interbeat intervals in response to feedback exposure between feedback conditions. Estimated Marginal Means (EMMs) for delta IBI's (in ms, referenced to IBI_{-2}) of control-, and negative-feedback trials, with IBI_0 being IBI closest to feedback exposure onset. Error bars depict the standard error of the means (SEMs), asterisks indicate significance levels.*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

7.6.5. EEG analysis

7.6.5.1. Standard setting for brainstorm

- SimNIBS settings
    - Vertex density : 0.5
    - Number of vertices on the CAT12 cortex surface : 15000
- DUNEURO settings
    - Source space : cortex surface
    - Forward modeling methods : DUNEuro FEM
    - FEM layers & conductivities
        - White matter : 0.14
        - Gray matter : 0.33
        - Cerebrospinal fluid : 1.79
        - Skull : 0.008
        - Scalp : 0.43
    - FEM solver type : Continuous Galerkin
    - FEM source model : Venant
    - Vennant options
        - Number of moments : 3
        - Reference length : 20
        - Weighting exponent : 1
        - Relaxation factor exponent : 6
        - Mixed moments : on
        - Restrict : on
    - Source space
        - Shrink source space : 0 mm
        - Force source space inside layer ‘gray’ : on
- Compute sources settings
    - Method : minimum norm imaging
    - Measure : current density map
    - Source model dipole orientations : constrained – normal to cortex
    - Depth weighting
        - Order : 0.5
        - Maximal amount : 10
    - Noise covariance regularization
        - Diagonal noise covariance
    - Regularization parameter
        - Signal-to-noise-ratio : 3.00
    - Output mode : inverse kernel only

7.6.5.2. All EEG results

Table (extra): All EEG results, regardless of significance. **Legend:** *ROI names*: names of the region investigated, if two names are given, it refers to the functional connection between both regions. *Sensor/Source*: denotes whether the measure is computed in sensor- or source space. *Fr. Band*: frequency band in which the measure is computed. $P_{uncorrected}$: uncorrected pvalue. $P_{FDRcorrected}$: corrected pvalue using the false discovery rate (FDR; Benjamini & Hochberg, 1995). *Models*: denotes the family of the models that best fit the data. *SES*: standardized effect size. *SE*: standard error. *Lower CI*: lower confidence interval. *Upper CI*: upper confidence interval. *FrontalMean*: mean of the six frontal electrodes (F7, F3, Fz, FPz, F4, F8). *Gamma*: gamma distribution. *Gaussian*: gaussian distribution.

ROI names	Sensor/Source	Fr. Band	$P_{uncorrected}$	$P_{FDRcorrected}$	Models	SES	SE	Lower CI	UpperCI
FrontalMean	Sensor	Theta	0,254	0,431	Gamma	0,014	0,012	0,037	0,010
FrontalMean	Sensor	Alpha	0,033	0,158	Gamma	0,033	0,016	0,002	0,064
FrontalMean	Sensor	Beta	0,423	0,553	Gamma	0,040	0,050	0,058	0,139
Ant_Insula_L	Source	Theta	0,143	0,326	Gamma	0,007	0,005	0,017	0,002
Ant_Insula_R	Source	Theta	0,647	0,756	Gamma	0,002	0,005	0,008	0,012
PCC_L	Source	Theta	0,903	0,931	Gamma	0,002	0,018	0,038	0,034
PCC_R	Source	Theta	0,839	0,879	Gamma	0,003	0,015	0,026	0,032
Precuneus_L	Source	Theta	0,093	0,270	Gamma	0,023	0,014	0,050	0,004
Precuneus_R	Source	Theta	0,368	0,525	Gamma	0,013	0,014	0,040	0,015
ACC_L	Source	Theta	0,158	0,330	Gamma	0,006	0,005	0,015	0,003
ACC_R	Source	Theta	0,763	0,838	Gamma	0,005	0,015	0,034	0,025
Orbitofrontal_L	Source	Theta	0,429	0,553	Gamma	0,007	0,009	0,025	0,011
Orbitofrontal_R	Source	Theta	0,937	0,952	Gamma	0,000	0,005	0,010	0,009
Ant_Insula_L	Source	Alpha	0,638	0,756	Gamma	0,006	0,014	0,033	0,020
Ant_Insula_R	Source	Alpha	0,355	0,517	Gamma	0,010	0,011	0,012	0,032
PCC_L	Source	Alpha	0,028	0,152	Gamma	0,056	0,026	0,006	0,106
PCC_R	Source	Alpha	0,000	0,000	Gamma	0,098	0,024	0,051	0,146
Precuneus_L	Source	Alpha	0,002	0,024	Gamma	0,074	0,024	0,027	0,121
Precuneus_R	Source	Alpha	0,000	0,000	Gamma	0,110	0,026	0,059	0,160
ACC_L	Source	Alpha	0,167	0,332	Gamma	0,025	0,018	0,011	0,061
ACC_R	Source	Alpha	0,103	0,276	Gamma	0,030	0,018	0,006	0,066
Orbitofrontal_L	Source	Alpha	0,417	0,553	Gamma	0,011	0,013	0,036	0,015
Orbitofrontal_R	Source	Alpha	0,085	0,270	Gamma	0,017	0,010	0,002	0,036
Ant_Insula_L	Source	Beta	0,746	0,838	Gamma	0,024	0,073	0,119	0,166
Ant_Insula_R	Source	Beta	0,782	0,845	Gamma	0,020	0,073	0,163	0,122
PCC_L	Source	Beta	0,174	0,332	Gamma	0,072	0,053	0,032	0,175
PCC_R	Source	Beta	0,298	0,476	Gamma	0,058	0,056	0,167	0,051
Precuneus_L	Source	Beta	0,149	0,326	Gamma	0,087	0,060	0,205	0,031
Precuneus_R	Source	Beta	0,029	0,152	Gamma	0,122	0,056	0,233	0,011
ACC_L	Source	Beta	0,044	0,184	Gamma	0,123	0,062	0,003	0,244
ACC_R	Source	Beta	0,042	0,184	Gamma	0,126	0,062	0,004	0,247
Orbitofrontal_L	Source	Beta	0,018	0,134	Gamma	0,170	0,072	0,028	0,311
Orbitofrontal_R	Source	Beta	0,097	0,270	Gamma	0,125	0,076	0,023	0,274
Ant_Insula_L-Precuneus_L	Source	Alpha	0,247	0,431	Gaussian	0,193	0,166	0,138	0,524
Ant_Insula_L-Precuneus_R	Source	Alpha	0,257	0,431	Gaussian	0,189	0,166	0,142	0,520

Ant_Insula_R-Precuneus_L	Source	Alpha	0,126	0,316	Gaussian	0,256	0,166	0,075	0,588
Ant_Insula_R-Precuneus_R	Source	Alpha	0,340	0,506	Gaussian	0,159	0,166	0,172	0,489
PCC_L-Precuneus_L	Source	Alpha	0,014	0,130	Gaussian	0,419	0,167	0,085	0,752
PCC_L-Precuneus_R	Source	Alpha	0,337	0,506	Gaussian	0,160	0,166	0,170	0,491
PCC_R-Precuneus_L	Source	Alpha	0,019	0,134	Gaussian	0,396	0,167	0,063	0,729
PCC_R-Precuneus_R	Source	Alpha	0,281	0,460	Gaussian	0,180	0,166	0,151	0,510
Precuneus_L-Precuneus_R	Source	Alpha	0,000	0,000	Gamma	0,079	0,011	0,058	0,099
Precuneus_L-ACC_L	Source	Alpha	0,096	0,270	Gaussian	0,279	0,166	0,052	0,611
Precuneus_L-ACC_R	Source	Alpha	0,050	0,198	Gaussian	0,329	0,167	0,003	0,662
Precuneus_L-Orbitofrontal_L	Source	Alpha	0,566	0,690	Gaussian	0,095	0,166	0,235	0,425
Precuneus_L-Orbitofrontal_R	Source	Alpha	0,091	0,270	Gaussian	0,283	0,166	0,048	0,615
Precuneus_R-ACC_L	Source	Alpha	0,453	0,573	Gaussian	0,125	0,166	0,205	0,455
Precuneus_R-ACC_R	Source	Alpha	0,313	0,488	Gaussian	0,168	0,166	0,162	0,499
Precuneus_R-Orbitofrontal_L	Source	Alpha	0,171	0,332	Gaussian	0,229	0,166	0,102	0,560
Precuneus_R-Orbitofrontal_R	Source	Alpha	0,407	0,553	Gaussian	0,138	0,166	0,192	0,468
Ant_Insula_L-Precuneus_L	Source	Beta	0,151	0,326	Gaussian	0,240	0,166	0,091	0,571
Ant_Insula_L-Precuneus_R	Source	Beta	0,405	0,553	Gaussian	0,139	0,166	0,192	0,469
Ant_Insula_R-Precuneus_L	Source	Beta	0,020	0,134	Gaussian	0,394	0,167	0,061	0,727
Ant_Insula_R-Precuneus_R	Source	Beta	0,059	0,219	Gaussian	0,318	0,167	0,014	0,650
PCC_L-Precuneus_L	Source	Beta	0,234	0,423	Gamma	0,015	0,012	0,039	0,010
PCC_L-Precuneus_R	Source	Beta	0,979	0,979	Gamma	0,000	0,012	0,023	0,023
PCC_R-Precuneus_L	Source	Beta	0,466	0,579	Gamma	0,007	0,010	0,027	0,012
PCC_R-Precuneus_R	Source	Beta	0,000	0,000	Gamma	0,025	0,005	0,014	0,035
Precuneus_L-Precuneus_R	Source	Beta	0,655	0,756	Gamma	0,005	0,011	0,027	0,017
Precuneus_L-ACC_L	Source	Beta	0,029	0,152	Gaussian	0,369	0,167	0,036	0,702
Precuneus_L-ACC_R	Source	Beta	0,012	0,130	Gaussian	0,425	0,167	0,091	0,759
Precuneus_L-Orbitofrontal_L	Source	Beta	0,811	0,862	Gaussian	0,040	0,166	0,370	0,290
Precuneus_L-Orbitofrontal_R	Source	Beta	0,233	0,423	Gaussian	0,199	0,166	0,132	0,530

Chapter 5

Similar and dissimilar neural activity along dimensions of psychosocial stress: an EEG source imaging study

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Abstract

The neural psychosocial stress response is investigated mainly using fMRI and many paradigms have been developed that employ various psychosocial stressors such as *ostracism* or *social-evaluative threat*. In contrast to comparing results of studies that employ the same paradigm, when fMRI results from different psychosocial stress paradigms are analyzed together, remarkably few brain regions can be identified that are consistently (de)activated. This lack of commonality in the neural stress response possibly indicates the specificity of the brain's response to distinct social threats, but might also be related to the indirect measurement of neural activity by fMRI. Therefore, in the current study, EEG was employed to investigate whether several commonly implicated brain regions of the psychosocial stress response exhibit clear similar or dissimilar changes in power or functional connectivity by employing a within-subjects design where participants were exposed to two psychosocial stress paradigms, the Cyberball and MIST. EEG data directly after stressor exposure was analyzed, thus investigating the recovery phase of the stress response. Results show that when analyzed together, neither similar nor dissimilar changes can be identified for any region, but if each paradigm is analyzed separately, significant changes are identified that are consistent with previous literature. The Cyberball results in power increases in the beta band for the left orbitofrontal, frontal, and temporal regions, and the MIST results in increased alpha activity of the left and right precuneus/PCC complex. The absence of results across both paradigms is possibly related to differences in emotion regulation following stressor exposure, but might also be due to the ineffectiveness of the Cyberball to elicit a stress response, as no change in the physiological response nor self-reported stress was found in this paradigm.

1. Introduction

The innate social nature of humans and the corresponding importance of healthy social relationships has been well established (Baumeister & Leary, 1995; Umberson & Karas Montez, 2010). Positive social connections throughout life are associated with improved physical and mental health, as well as decreased mortality, while the absence of a nurturing social environment results in worse health outcomes (J. T. Cacioppo & Cacioppo, 2014; Orben et al., 2020; Umberson et al., 2010; J. Wang et al., 2018). Given the strong reliance of humans on their social environments, stimuli that might threaten these environments, called *psychosocial stressors*, are logically deemed aversive and are met with a bodily response to overcome or adapt to the perceived threat, the so-called stress response (Epel et al., 2018; Folkman & Lazarus, 1984).

Although psychosocial stressors can be understood as *any threatening stimuli originating from unpredictable or uncontrollable social interactions* (Folkman & Lazarus, 1984; Koolhaas et al., 2011; Vanhollebeke et al., 2022), the term encompasses a large variety of stimuli that affect different aspects of social interactions, possibly resulting in distinct stress responses. The identification of different psychosocial stressors and subsequent development of experimental paradigms to investigate their isolated effects has consequently resulted in a more refined understanding of the social stress response (Muscatell et al., 2021). This refinement has led to the conceptualization and description of several specific psychosocial stressors, of which *social-evaluative threat* (Dickerson, 2008) and *ostracism* (Williams, 1997, 2007) are possibly the best-known.

Social-evaluative threat (SET) arises from situations where an individual could be judged negatively by others (Dickerson, 2008) and can be investigated with paradigms such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005). *Ostracism* is present when the individual is excluded or ignored from social interactions and is most commonly examined with the Cyberball paradigm (Williams et al., 2000). Both psychosocial stressors have obvious similarities but evoke surprisingly distinct psychophysiological responses. While both elicit significant psychological changes (Hartgerink et al., 2015; Linares et al., 2020; Williams, 2007), paradigms employing SET result in consistent physiological responses (mainly identified with increases in cortisol), that are not consistently found when the Cyberball paradigm is used (Helpman et al., 2017; Liu et al., 2017; Zöller et al., 2010).

This principle of similarity and dissimilarity is also encountered using neuroimaging (McEwen, 2007, 2009; Muscatell et al., 2021). In a recent meta-analysis of functional magnetic resonance imaging (fMRI) studies investigating psychosocial stress, Berretz and colleagues (2021) found that when studies that employ the Cyberball paradigm are taken together with studies employing different psychosocial stressor paradigms (i.e., the aversive viewing paradigm (Henckens et al., 2009), social-evaluative threat paradigm (Eisenbarth et al., 2016), MIST (Dedovic et al., 2005) and ScanStress (Lederbogen et al., 2011)), *two* clusters of increased neural activation can be identified: the left and right (i.e., bilateral) anterior insula combined with the claustrum and parts of the inferior frontal gyrus (IFG), and one cluster of decreased activity encompassing the right amygdala and part of the parahippocampal gyrus. However, when the Cyberball paradigm is not included, *five* activation clusters are identified: again the bilateral anterior insula with parts of the IFG and the claustrum, but now also the right lentiform nucleus and thalamus, the precentral gyrus with parts of the posterior insula, and the inferior/middle temporal gyrus combined with the middle occipital gyrus. Additionally, *three* clusters of deactivation are identified: the parahippocampal gyrus, the precuneus and posterior cingulate cortex (PCC), and the superior temporal gyrus (Berretz et al., 2021). These separate meta-analyses again identify the Cyberball as an outlier regarding psychosocial stressors. Similarly, in a recent fMRI study employing a within-subjects design where participants were exposed to both the MIST and the Cyberball, increased functional connectivity was found between the amygdala and medial prefrontal cortex (mPFC) after Cyberball exposure in females, but not after the MIST, again hinting at the fact that different psychosocial stressors evoke distinct neural reactions (Bürger et al., 2023).

Although fMRI has been a seminal tool for the investigation of the neural correlates of psychosocial stress, clearly evident from the previous paragraph, two inherent limitations of the technique limit its ability to fully measure neural activity, therefore possibly missing additional (dis)similarities of the psychosocial stress response. Firstly, its limited temporal resolution (order of seconds) makes it impossible to capture faster aspects of neuronal activity (order of milliseconds). Secondly, fMRI measures neural activity indirectly through changes in oxygenated blood in the brain, the so-called blood-oxygen-level-dependent (BOLD) signal (Logothetis, 2008). This indirect measurement results in a reduced, simplified window into neural activity whereby parts of the brain are interpreted as either more (i.e., an increased BOLD signal) or less (i.e., a decreased BOLD signal) active, while the underlying neural processes are more complex (Ekstrom, 2010; Heeger & Ress, 2002; Logothetis, 2008; Theriault et al., 2023).

This conceptualization of neural activity may hinder the comparison of neuronal stress responses because different neural processes within certain brain regions possibly result in similar interpretations of either increased or decreased activity. Therefore electro-encephalography (EEG), while having inferior spatial resolution compared to fMRI, has been increasingly used to uncover additional aspects of the neural psychosocial stress response (Giannakakis et al., 2019; Katmah et al., 2021; Vanhollebeke et al., 2022). Contrary to fMRI, EEG measures neuronal activity directly by capturing the small potential differences at the scalp of an individual from pyramidal neuron activity (Cohen, 2017). This more direct assessment of neural activity combined with the high temporal resolution of EEG provides a unique possibility to investigate potential similar or differential activation patterns within brain regions commonly associated with the neuronal psychosocial stress response.

Therefore, to investigate possible similar or differential neuronal activations of several key brain regions across psychosocial stressors, we exposed participants to two different psychosocial stressor paradigms, Cyberball and MIST, while continuously recording EEG data. To compare the neuronal responses to both stressors as best as possible, resting-state, eyes-closed EEG data captured directly after stressor exposure is compared to EEG data captured directly after an active control condition in each paradigm. The so-called *recovery phase* of the stress response (Vanhollebeke et al., 2022) is thus investigated. Employing EEG source imaging (ESI; i.e., the mathematical process of projecting measured neural activity at the scalp to the responsible sources within the brain; Michel & Brunet, 2019) five brain regions (see above) in each hemisphere, selected based on literature, will be investigated. These regions are the *anterior insula with parts of the IFG* (Berretz et al., 2021; Dedovic et al., 2009; Kogler et al., 2015; H. Wang et al., 2017), the *precuneus/PCC complex* (Berretz et al., 2021; Mwilambwe-Tshilobo & Spreng, 2021; van Oort et al., 2017; Vanhollebeke, Kappen, et al., 2023), the *orbitofrontal cort*ex (S. Cacioppo et al., 2013; Dedovic et al., 2009; Mwilambwe-Tshilobo & Spreng, 2021; Vijayakumar et al., 2017), parts of the *frontal cortex* (Berretz et al., 2021; Dedovic et al., 2009; H. Wang et al., 2017), and parts of the *temporal lobe* (Dedovic et al., 2009; Kogler et al., 2015; Mwilambwe-Tshilobo & Spreng, 2021; J. Wang et al., 2018). For each region, relative power in the alpha (8-13 Hz) and beta (13-30 Hz) frequency ranges will be computed, given that these frequency ranges seem to be the most sensitive to psychosocial stressors (Giannakakis et al., 2019; Katmah et al., 2021; Vanhollebeke et al., 2022). Aside from relative power, functional connectivity (FC, the measurement of temporal dependencies between spatially separated brain regions, Friston, 1994) between the brain regions will be

assessed using amplitude envelope correlation (AEC; Colclough et al., 2016; Hipp et al., 2012) in the aforementioned frequency ranges. Additionally, both state questionnaire (assessing feelings of negative affect (NA); Gilbert et al., 2008; Petrocchi et al., 2017, and self-reported stress) and physiological data (electrocardiography (ECG) and electrodermal activity (EDA) data) were collected to assess the psychological and physiological response of the participants to the aforementioned psychosocial stressors. Contrary to the recovery phase investigated using EEG, the physiological response is evaluated during the active control and stress phase, thus evaluating the *reactive* phase for the effectiveness of the paradigms (Vanhollebeke, Kappen, et al., 2022).

For the state questionnaire data, we hypothesize that both NA and stress will increase after stressor exposure for both paradigms. Regarding physiological activity, we hypothesize that decreased parasympathetic activity, identified by decreased root mean square of successive differences between heartbeats (RMSSD; Kim et al., 2018) and increased sympathetic activity, indexed by the skin conductance response rate (SCRR; Giannakakis et al., 2019), during stressor exposure will be found in the MIST, but not in the Cyberball paradigm, similarly to the cortisol results identified in earlier research (Helpman et al., 2017; Liu et al., 2017; Zöller et al., 2010). For the EEG power data, we hypothesize a main effect (i.e., a significant change in power for both paradigms in the same direction, indicating the effect of psychosocial stressors as a unified concept) of increased beta power in the bilateral anterior insulae (Berretz et al., 2021). Additionally, we hypothesize an interaction effect (i.e., changes in EEG power depending on the employed paradigm, reflecting effects specific to either SET or ostracism) in the precuneus/PCC complex where we expect an increased alpha power in the precuneus/PCC complex during the MIST paradigm (Vanhollebeke, Kappen, et al., 2023), and have no additional hypotheses. Regarding the functional connectivity results, we also have no specific hypotheses. Finally, each paradigm will be analyzed separately in an explorative manner.

2. Materials and methods

2.1. Participants

A convenience sample of 73 healthy, adult participants (13 men, 60 women) was recruited through advertisements on social media. Participants were excluded if they were younger than 18 or older than 45, were pregnant, had (a history of) psychiatric disorders or a current depressive episode, had a substance addiction (nicotine and caffeine not considered), had an eye, heart, or respiratory disorder, or had participated in an earlier study (Vanhollebeke, Kappen, et al., 2023). Additional exclusion criteria related to EEG were a family history of epilepsy, recent neurosurgical procedures, pacemaker or other electronic implants, inner ear prosthesis, metal objects in the brain or around the head, skin conduction on the head, current use of psychotropic medication,neurological problems, and dreadlocks. (see section 6.5.1.). Participants were further asked to refrain from smoking or drinking coffee for up to 2 hours before the start of the experiment. Seventy-three participants completed the Cyberball paradigm and 66 participants completed the MIST paradigm. Based on the quality of the obtained EEG data (see section 2.5.2. for further information), ten participants were further excluded from the Cyberball dataset and 13 participants were excluded from the MIST dataset. This resulted in 63 participants (13 men, 50 women; M_{AGE} = 21.44; SD_{AGE} = 2.9, range = [18, 30]) for the Cyberball paradigm and 53 participants (9 men, 44 women; M_{AGE} = 21.49; SD_{AGE} = 2.95, range = [18, 30]) for the MIST paradigm, where all participants for the MIST had also participated in the Cyberball. The study was conducted according to the declaration of Helsinki and ethical approval was obtained from the Ghent University medical ethical committee (registration number: B6702020000676). All participants gave written informed consent before the start of the study (online) and before the start of the first on-site data collection (in person), and were debriefed on the purpose of the study after the second in-person data collection. After completion of the complete experiment, participants received a 40 euro compensation fee through bank transfer.

2.2. Experimental procedure

The current study is part of a larger project investigating the effect of psychosocial stress reactivity and recovery and not all collected data is discussed in the current article. The results of collected speech data are described in another article (Kappen et al., 2023).

2.2.1. Study procedure

An overview of the study is shown in Figure 1. After a possible participant contacted the experimenters and was approved to participate, they filled in an online informed consent and several trait questionnaires (not discussed further) using the online platform LimeSurvey (Schmitz, 2012). In-person data was collected in a dedicated room at the Department of Adult Psychiatry of the Ghent University Hospital. At the start of the first on-site data collection moment, participants again signed the informed consent (on paper), the experimenters explained the cover story (see section 2.2.2.), and answered any further questions. Afterward, both on-site moments expired similarly, with the main difference being the task that was to be performed. After ECG and EDA electrodes, and EEG cap placement (10-30 minutes), participants were seated before a computer screen and were instructed to sit as still as possible. Firstly participants rested for 10 minutes (first five minutes with their eyes closed, second five minutes with their eyes open where participants looked at a cross at the center of the screen), after which they filled in a state questionnaire (2 minutes, see section 2.3.). Subsequently, they were introduced to the task (Cyberball on day one, see section 2.2.3.; MIST on day two, see section 2.2.4.) and performed the control condition (Cyberball: inclusion phase (10-15 minutes); MIST: control phase (10-15 minutes)). Immediately after the control condition, a state questionnaire was again filled in after which a 10-minute rest (five minutes eyes closed, five minutes eyes open) and a third state questionnaire was completed. Afterward, the second part of the paradigm was introduced and completed (Cyberball: exclusion phase (10-15 minutes); MIST: stress phase (10-15 minutes)), after which a fourth state questionnaire was completed. A third rest period (identical to the previous two) followed after which a final state questionnaire was collected. Both experiments were programmed in OpenSesame (Version 3.2.8.; Mathôt et al., 2012). At the end of day 2, participants were debriefed and payment information was collected.

2.2.2. Cover story

Participants were told that the current study investigated whether brain networks related to mental imagery (a common cover story for the Cyberball paradigm; Vanhollebeke, Aers et al., 2023) were also involved when individuals solve mathematical equations, given that some people “imagine” the different mathematical steps. Participants were told that, in order to investigate this, they would play a ball-tossing game (Cyberball paradigm) first, and would solve mathematical equations on the second day (MIST paradigm). They were asked to try to imagine tossing the ball as best as possible. If participants asked upon completing the Cyberball

whether the confederates were real or not because they felt excluded, experimenters told them that this was not intended and that it would be looked into. After completion of the MIST, participants were told the real goal of the study.

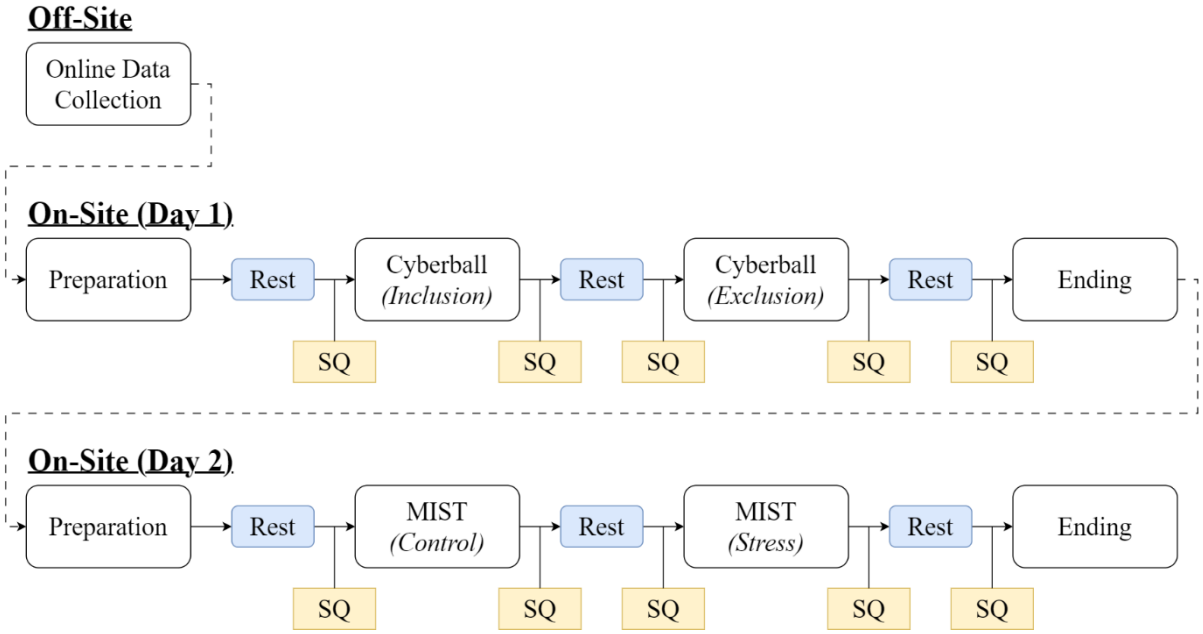

Figure 4: Overview of the study paradigm. *Rest* = rest condition, composed of five minutes where the participant has their eyes closed, and five minutes where the participant has their eyes opened; SQ = State Questionnaire.

2.2.3. Cyberball

During the Cyberball paradigm, participants tossed a ball between themselves and two confederates, and participants were told that the other participants were at other universities. The confederates were however computer-generated and their behavior was pre-defined (Williams et al., 2000). The paradigm was visualized by a picture of the participant at the bottom center (sent by the participant beforehand and deleted after the participant completed the paradigm) while the two confederates (one male, one female, relative location to the participant counterbalanced across participants) were represented by pictures framed in a black square (Allaert et al., 2022). Participants were able to throw the ball to the left or right confederate by pressing the corresponding arrow key with their right hand. The movement of the ball took 1500 ms. When a confederate was in possession of the ball, the ball remained with the confederate for two to three seconds (randomized) before the ball was thrown again to imitate the thought processes of the confederates. **Inclusion Phase:** the inclusion phase consisted of 150 throws, where participants received the ball 33% of the time. **Exclusion Phase:** the exclusion phase consisted of an initial normal (inclusion) phase (30 throws) where participants received the ball 33% of the time. After 30 throws, the participant was excluded partially for the remaining 120

throws in a probabilistic manner where the chance of receiving the ball increased with each consecutive throw not directed at the participant (chances of retrieving the ball: 0, 0, 0.16, 0.16, 0.33, 0.33, 0.66, 0.66, 1). This lead to a ball receival chance of 17-18% (validated through simulation, see OSF for the code: https://osf.io/hv6uw), which is commonly employed in EEG-compatible Cyberball studies (Vanhollebeke, Aers, et al., 2023).

2.2.4. Montreal imaging stress task

During the Montreal Imaging Stress Task (MIST), participants were asked to solve mathematical questions of increasing difficulty (Dedovic et al., 2005). Mathematical equations were shown in black on a white background and the correct answer always was a number from zero to nine, and participants could answer each question by pressing the corresponding number on the Numpad of the keyboard with their right hand. The difficulty scales are identical to the original article and the code to generate the equations was graciously provided by Professor Pruessner and adapted to MATLAB for further usage (Dedovic et al., 2005).

Control Phase: the control phase consisted of seven difficulty scales for exercises. In each scale, the participant was able to solve up to ten equations and each scale ended when either the participant solved all equations, or more than 2 minutes passed. Depending on the answer of the participant, after each equation either *Correct!* (correct response), *Incorrect!* (incorrect response), or *Timeout!* (participant did not answer in time) was shown in black on the screen. For each difficulty scale, the average time it took the participant to solve equations was obtained. **Stress phase:** the stress phase employed the same difficulty scales as the control condition (with different equations), but differed in the introduction to the task phase, the allowed time for each equation and the presentation of the equations, and the feedback participants received after each given answer. Before the start of the stress phase, participants were told (as part of the cover story) that their responses would now be compared to a group and that they should score at least up to the average score (based on time and correctness), or else their data would not be eligible for further analyses. When presented with an equation, participants now saw a black, shrinking bar above the equation indicating the remaining time to solve the equation. The allowed time for each equation was set to be 90% of that participant's average response time for the equations of the same difficulty scale during the control phase, conforming to the original MIST procedure (Dedovic et al., 2005). When participants solved three successive equations correctly, the allowed time was further reduced by 10%, and three successive incorrect answers resulted in an increase of 10% of the allowed time. Below the equation, participants also saw a performance bar (three colors from left to right: red, yellow,

and green) with two arrows indicating both the personal and average scores. The personal score arrow was moved by 5% of the total performance bar length after each equation (incorrect answer or timeout: moved to the left; correct answer: moved to the right). The average score arrow location was stationary and indicated an average performance of 83%. The feedback (*Correct!*, *Incorrect!*, *Timeout!*) did not differ between the control and stress phase. Finally, after the participant completed five difficulty scales and their performance was below the average performance, the experiment paused and the experimenter reminded the participant to improve their performance or otherwise their data could not be used.

2.3. State questionnaires

The state questionnaire that was used assessed positive affect (both activating (APA) and soothing (SPA)) and negative affect (NA; Gilbert et al., 2008; Petrocchi et al., 2017). Each aspect was probed by six questions ("Right now, how much do you feel [prompt]?"), rated on a visual analogue scale (range = [0, 100], with "Not at all" at the left of the VAS and "Very" right of the VAS). NA was assessed by *upset, distressed, scared, angry, anxious*, and *sad*; APA was assessed by *lively, energetic, active, enthusiastic, dynamic*, and *excited*; SPA was assessed by *relaxed, serene, content, calm, tranquil*, and *peaceful*. Aside from the questionnaire, an additional item (*stressed*) was asked to probe whether the participants were stressed throughout the paradigms. Only the negative affect and stress questions will be discussed further.

2.4. Physiological analysis

Both electrocardiography (ECG) and electrodermal activity (EDA) were collected throughout the paradigms using the VU-AMS ambulatory monitor (Vrije University Amsterdam, www.vu-ams.nl, Amsterdam, the Netherlands). ECG data was collected using three electrodes, one placed between the right lower two ribs (ground), one placed at the left lateral side of the chest at the height level of the xiphoid process (V+), and one slightly below the right collar bone four to five cm right from the sternum (V-). EDA data was collected by placing two velcro electrodes (with applied isotonic electrode gel; Biopac) on the middle phalanges of the left index- and middle finger. Data during the active control and stress phase were analyzed.

2.4.1. ECG analysis

ECG data was preprocessed using a custom Python script[1]. The raw ECG data (1 kHz) is resampled at various frequencies and for each signal the R-peaks are detected. If peak locations across the signals were less than 25 milliseconds separated, they were considered as a single peak whose time is defined as the earliest time it has been detected. To assure that the detected peak is not an artifact in the signal, only peaks that were detected in more than 80% of the signals were considered true peaks. Visual validation demonstrated the robustness of this approach to our ECG data. For subsequent detected peaks, the R-R peak intervals (unit: milliseconds) were obtained, from which the root mean square of successive differences (RMSSD) was computed.

2.4.2. EDA analysis

EDA data was preprocessed using a custom Python script (see Kappen et al., 2023). The data was first filtered using a 2 Hz low-pass filter, after which it was decomposed into its tonic and phasic components. Subsequently, the skin conductance response rate (SCRR) was computed from the phasic component by identifying peaks using the *find_peaks* function (*scipy* package). The threshold values for the rise and fall time and peak parameters were determined based on guidelines in the literature (Posada-Quintero & Chon, 2020).

2.5. EEG analysis

2.5.1. Equipment

Brain activity was continuously recorded at 127 locations across the scalp (matched to the international 10-10 system; Luu & Ferree, 2005) using the EGI 130 HydroCel Geodesic Sensornet (HCGSN 130) with Ag/AgCl electrodes and the Net Amp 400 amplifier from EGI (Magstim-EGI Inc., Eugene, OR, USA). EEG data was recorded at 1 kHz with Cz as online reference. Throughout each recording, electrode impedances were kept below 50 kΩ.

2.5.2. Preprocessing

The EEG data were downsampled to 200 Hz, high-pass filtered at 0.1 Hz, and converted to European Data Format (EDF) using the Net Station software (version 5.4., Magstim-EGI Inc., Eugene, OR, USA). Further preprocessing was conducted using Brainvision Analyzer (version

[1] : https://github.com/mitchelkappen/stress_cyberball-mist/blob/main/cybb_mist/ecg_processing.py

2.1., Brain Products GmbH, Gilching, Germany). First, an electrode coordinate transformation was performed from EGI's cartesian coordinate system to the polar coordinate system (for more information, see https://osf.io/jkat6). Second, data were bandpass filtered (low-pass cutoff = 0.5 Hz; high-pass cutoff = 40 Hz; 48 dB/octave) and net line electrical noise was removed using a Notch filter at 50 Hz. Third, electrodes below the eyes were removed (channels 126, 127), and bad channels (identified by visual inspection) were interpolated using spline interpolation (order = 4; lambda = 1e-5). Afterward, the eyes-closed, resting-state segments (five minutes each) were segmented from the rest after the control condition, and rest after the stress condition (see figure 1) and the following steps were conducted for each segment separately. Artifacts related to eye movement were removed using an automated independent component analysis (ICA) procedure. Data from electrodes directly above the eyes were used to detect blinks and blinks were identified by a sudden increase in slope. When blinks were detected, 30% of global field power was removed (standard setting BrainVision). The remaining artifacts were further identified by a min-max (maximum voltage range of 200 μV/200 ms), gradient (maximum voltage change of 50 μV/ms), and low voltage (minimum voltage change of 0.5 μV/100 ms) criterion. If detected, data 200 ms before and after the artifact was flagged. Data was subsequently divided into epochs of 3 seconds, and epochs containing flagged data were omitted. The remaining data were re-referenced to the average reference and exported in EDF+ format, and can be found on OSF (link: https://osf.io/t28rn). Only participants from which at least 10 epochs in each condition were available were used for further analysis (for an overview, see: https://osf.io/sz4yh).

2.5.3. Source level analysis

2.5.3.1. Source modeling

To conduct the EEG source modeling, the Brainstorm toolbox was used (version 3.220517, Tadel et al., 2011). Before using Brainstorm, the EDF+ data was transformed into .mat files (these can be found on OSF; link: https://osf.io/t28rn) and subsequently imported into Brainstorrm. Given that no individual MRI images were available, the USCBrain (and complementary T1 MRI image) atlas was used (Joshi et al., 2022). First, the headmodel was constructed using the *mri2mesh* finite element modeling (FEM) method from the SimNIBS toolbox (Thielscher et al., 2015; Windhoff et al., 2013). Using the standard settings (0.5 nodes/mm² of surface mesh; 15000 vertices on the cortex surface), a 642359 vertex FEM mesh with five layers (skin, skull, gray matter, white matter, cerebrospinal fluid) was obtained. Secondly, the electrodes were co-registered to the headmodel using LPA, RPA, Cz (= Reference

electrode; EGI), Fpz (= electrode 17; EGI), and Oz (= electrode 75; EGI) as references. Dipoles were defined in the gray matter (evenly spaced at 5mm; 15269 in total) and the leadfield matrix was obtained using the DUNEURO toolbox with standard settings (see section 6.5.2.; Medani et al., 2021). The inverse problem was solved by constraining the orientation of the dipoles to be normal to the cortical surface and subsequently computing current density maps (unit: Ampere-meters) with the weighted minimum norm estimation (wMNE) method where sensor noise was estimated using the diagonal of the noise covariance matrix, and standard settings for depth weighting and regularization were used. Afterward, the time series for all regions in the USCBrain atlas (130 in total) were computed by taking the mean value of all dipoles linked to each region. These time series were extracted from Brainstorm and converted to .mat objects (which can be found on OSF; link: https://osf.io/t28rn).

2.5.3.2. Mapping of brain regions

Based on previous research, five brain regions in each hemisphere were selected for study. The mapping of the brain regions of interest to USCBrain scouts is shown in table 1.

Table 3: Mapping of the brain regions of interest to scouts of the USCBrain atlas (Joshi et al., 2022).

Brain ROI	**USCBrain Scouts (L)**	**USCBrain Scouts (R)**
Anterior Insula	Insula – anterior L	Insula – anterior R
	Pars Triangularis – Anterior L	Pars Triangularis – Anterior R
	Pars Triangularis – Middle L	Pars Triangularis – Middle R
	Pars Triangularis – Posterior L	Pars Triangularis – Posterior R
PCC/Precuneus	Cingulate Gyrus – Posterior L	Cingulate Gyrus – Posterior R
	Precuneus – Inferior L	Precuneus – Inferior R
Orbitofrontal Region	Anterior Orbitofrontal Gyrus L	Anterior orbitofrontal gyrus R
	Middle Orbitofrontal Gyrus L	Middle Orbitofrontal Gyrus R
	Posterior Orbitofrontal Gyrus L	Posterior Orbitofrontal Gyrus R
	Gyrus Rectus L	Gyrus Rectus R
Frontal Region	Middle Frontal Gyrus – Posterior L	Middle Frontal Gyrus – Posterior R
	Superior Frontal Gyrus – Posterior L	Superior Frontal Gyrus – Posterior R
Temporal Region	Middle Temporal Gyrus – Middle L	Middle Temporal Gyrus – Middle R
	Middle Temporal Gyrus – Dorsoposterior L	Middle Temporal Gyrus – Dorsoposterior R
	Middle Temporal Gyrus – Ventroposterior L	Middle Temporal Gyrus – Ventroposterior R
	Superior Temporal Gyrus – Middle L	Superior Temporal Gyrus – Middle R
	Superior Temporal Gyrus – Posterior L	Superior Temporal Gyrus – Posterior L

2.5.3.3. Power analysis

Relative power for the alpha (8 - 13 Hz) and beta (13 - 30 Hz) frequency range was computed for all regions of interest (see table 1). First, the power of the whole considered frequency spectrum (1 - 40 Hz) and the two defined frequency bands were computed using Welch's spectral power density and corrected for 1/f noise with a correction exponent of one (Cohen, 2014). Secondly, the power of the considered frequency band was divided by the power of the whole frequency spectrum, resulting in a single value (range = [0, 1]) that can be understood as the percentage of total power that is present in the defined frequency range. This computation was conducted for each epoch separately and the resulting power values were averaged to obtain an average power value. These analyses were conducted using custom MATLAB code that can be found on OSF (link: https://osf.io/t28rn).

2.5.3.4. Functional connectivity analysis

The functional dependencies in the alpha (8 - 13 Hz) and Beta (13 - 30 Hz) frequency range between the considered brain regions were assessed using amplitude envelope correlation (AEC). AEC is an undirected, bivariate FC measure that assesses linear dependencies between brain regions by investigating the similarities in amplitude changes within a specific frequency range throughout time (Brookes et al., 2011, 2012; Colclough et al., 2016; Hipp et al., 2012). In order to calculate AEC, the time series of two brain regions were filtered with a bandpass filter, thus only considering oscillations within a predefined frequency range. Subsequently, the bandpassed time series were pairwise orthogonalized using a stabilized Gram-Schmidt algorithm to minimize the influence of spatial leakage introduced by the source modeling procedure (Hedrich et al., 2017). Given that the orthogonalization procedure is non-symmetric (i.e., results are dependent on the order of time series), orthogonalization was performed twice, and subsequent described operations were performed for each pair of orthogonalized signals separately, after which the obtained results were averaged to obtain a single value. After orthogonalization, the amplitude envelopes of each signal were obtained by taking the absolute value of the Hilbert-transformed signal. Finally, the correlation between both amplitude envelopes was computed. AEC thus results in a single correlation value (range = [-1, 1]), where larger values (regardless of the sign) indicate more functional connectivity between two brain regions. The functional connectivity analyses were conducted using custom MATLAB code that can be found on OSF (link: https://osf.io/t28rn).

2.6. Statistical analysis

The statistical analysis was conducted using R (version 4.3.0.) in RStudio (version 2022.2.1.461). All information regarding the analysis and the script itself can be found on OSF (information: https://osf.io/a5kzs; Questionnaire script: https://osf.io/ymhwb; Physiological script: https://osf.io/ytbv2; EEG main effect script: https://osf.io/hj2p6; EEG interaction effect script: https://osf.io/3nkrc; EEG exploratory script: https://osf.io/etxaq).

2.6.1. State quesionnaires

A linear mixed model (LMM) was constructed using the R package *lme4* where the response of either the negative affect (NA) or the stress question(s) was the dependent variable, the paradigm (Cyberball and MIST) and the condition (control and stress) were fixed effects with interaction, and the participant ID was a random intercept. (R formula: *State_Questionnaire ~ Paradigm * Condition + (1|Participant_ID)*. Model significance (*p-value* < 0.05) was assessed with an ANOVA (type III, *car* package) test and estimated marginal means (EMMs) were subsequently obtained using the *emmeans* function (*emmeans* package). From the EMMs the beta coefficient, t-, and p-value from the *condition* contrast were extracted. Effect sizes (Cohen's D), regardless of significance, together with their corresponding 95% confidence intervals (CIs) were computed (*eff_size* function, *emmeans* package) for further insight into the results. If results were significant, the possible added value of sex was assessed by constructing a model but with the sex variable as a fixed effect (R formula: *State_Questionnaire ~ Paradigm * Condition + Sex + (1|Participant_ID)*). Both models were subsequently compared using a χ^2 goodness-of-fit test (using the *anova* function). If no significant difference was found (i.e., the *p-value* of the χ^2 test was greater than 0.05) it was concluded that sex did not improve the model fit and, given the preference for parsimonious models (Bates et al., 2018), was subsequently not included as a factor in the model.

2.6.2. Physiological data

The statistical analysis for the physiological data was conducted similarly to the questionnaire data where either RMSSD or SCRR was the dependent variable, paradigm and condition were fixed effects with interaction, and participant ID was a random intercept (R formula: *Physiological_Variable ~ Paradigm * Condition + (1|Participant_ID)*). All subsequent analyses were conducted identically to section 2.6.1.

2.6.3. EEG data

2.6.3.1. Power analysis

The analysis of the EEG power data was conducted in two steps. Firstly, the *main effect* of condition (i.e., control compared to stress) was assessed by constructing an additive model (R formula: *Power ~ Paradigm + Condition + (1|Participant_ID)*) which did not consider possible interactions between paradigm and condition, given that main effects can not easily be interpreted if interactions are taken into account (Brambor et al., 2006). From this model, the *condition* contrast is obtained and subsequent analysis steps are identical to section 2.6.1.

To investigate *interaction* effects, LMMs with the R formula: *Power ~ Paradigm * Condition + (1|Participant_ID)*) were constructed. Given that possible main effects have already been investigated, only the interaction effect was tested using ANOVA (type III) and only models with significant interaction effects were further considered. Subsequent analyses were conducted identically as section 2.6.1.

Finally, the exploratory analyses of each paradigm separately were conducted similarly as before, but now the paradigm factor is not included as a fixed effect, and instead, LMMs were constructed for each paradigm separately, with the R formula: *Power ~ Condition + (1|Participant_ID)*).

2.6.3.2. Functional connectivity analysis

Given the many possible functional connections (180 in total, 45 for each frequency range/paradigm combination), only functional connections between brain regions whose power changed significantly were considered. Aside from this restriction, the analysis was conducted identically to the power analysis, where the functional connectivity values were the dependent variable, the condition a fixed effect, and participant ID a random intercept (R formula: *FC ~ Paradigm * Condition + (1|Participant)*).

2.6.4. Multiple comparison correction

Tests were corrected for multiple comparisons using the false discovery rate method (FDR; Benjamini & Hochberg, 1995). Tests for each measuring modality (i.e., self-report questionnaires, and physiological data) were grouped together and corrected. For the tests related to the EEG data, tests were grouped according to the effect type (i.e., main or interaction effect) and frequency range that was investigated (i.e., alpha or beta frequency band).

3. Results

3.1. State questionnaires

3.1.1. Negative affect

A significant increase in negative affect is found in both the Cyberball paradigm (β = 5.42; SE = 1.56; t = 3.45; p = 0.001; d = 0.62; CI = [0.26, 0.97]) and the MIST paradigm (β = 4.79; SE = 1.71; t = 2.8; p = 0.008; d = 0.54; CI = [0.16, 0.93]), confirming our hypothesis. Sex did not improve the model fit (p > 0.9). These results can be found in Figure 2.

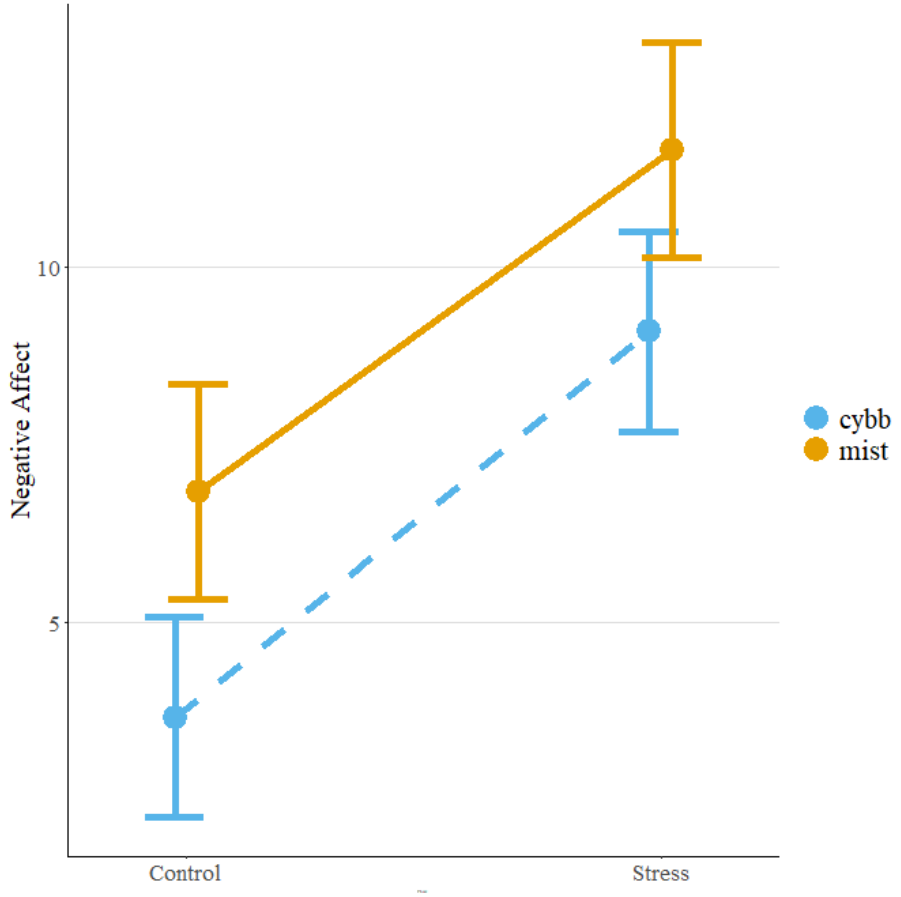

Figure 5: Visualization of the estimated marginal means (EMMs) for the self-reported Negative Affect. **Note:** The error bars show the standard error of the means (SEMs).

3.1.2. Stress

No significant difference in self-reported stress was found in the Cyberball paradigm (β = 4.55; SE = 3.53; t = 1.29; p = 0.2; d = 0.23; CI = [-0.12, 0.58]), contradicting our hypothesis. However, in the MIST paradigm, a significant increase was identified (β = 19.85; SE = 3.85; t = 5.14; p < 0.001 ; d = 1; CI = [0.6, 1.39]), confirming our hypothesis. Sex did not improve model fit (p = 0.09). These results are shown in Figure 3.

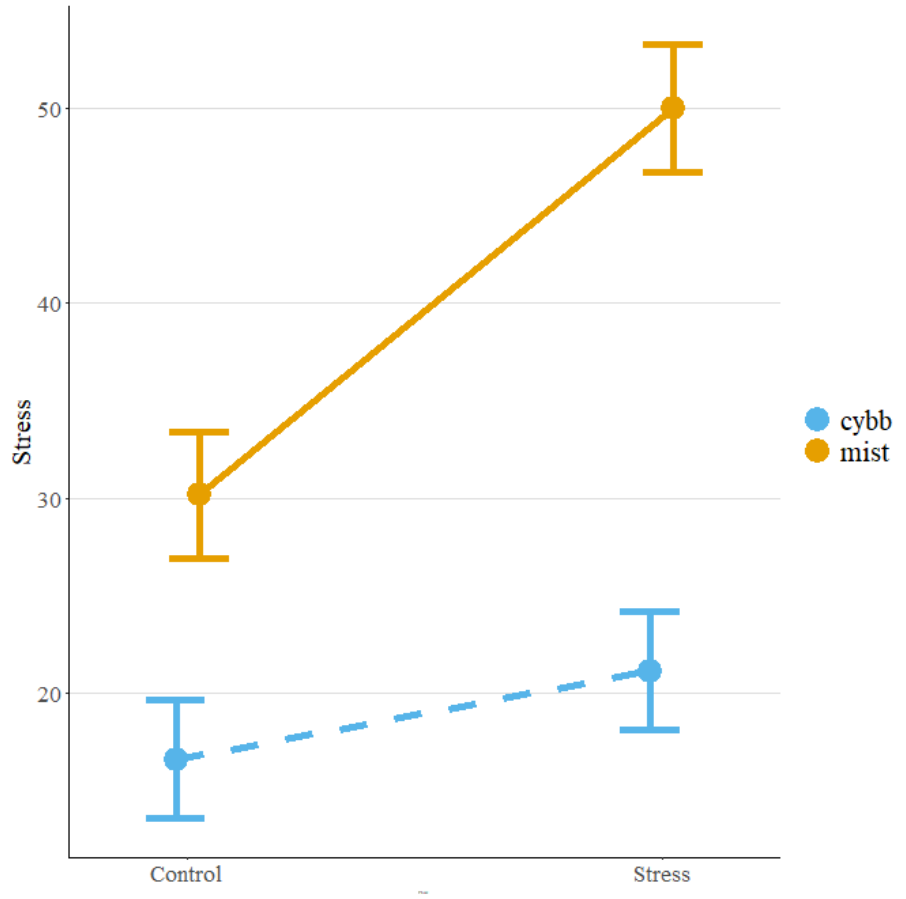

Figure 3: Visualization of the estimated marginal means (EMMs) for the self-reported Stress. **Note:** The error bars show the standard error of the means (SEMs).

3.2. Physiological data

3.2.1. RMSSD

RMSSD changes were not significant for either the Cyberball paradigm ($\beta = 4.55$; $SE = 3.05$; $t = 1.49$; $p > 0.18$; $d = 0.29$; $CI = [-0.09, 0.67]$) or the MIST paradigm ($\beta = 3.24$; $SE = 3.26$; $t = 0.99$; $p > 0.32$; $d = 0.21$; $CI = [-0.2, 0.62]$). Therefore our hypotheses were partly confirmed. Sex did not improve the model performance ($p > 0.48$). Given the insignificance, these results are not shown in the article, but can be found in the supplemental materials (section 6.5.3.).

3.2.2. SCRR

A significant increase in SCRR was identified in the MIST paradigm (β = 1.3; *SE* = 0.37; t = 3.52; p = 0.002 ; d = 0.71; *CI* = [0.31, 1.12]), but was not found in the Cyberball paradigm (β = 0.65; *SE* = 0.33; t = 1.93; p > 0.11; d = 0.36; *CI* = [-0.009,0.72]), confirming our hypothesis. Sex had no significant influence on the model performance (p > 0.6). These results are shown in Figure 4.

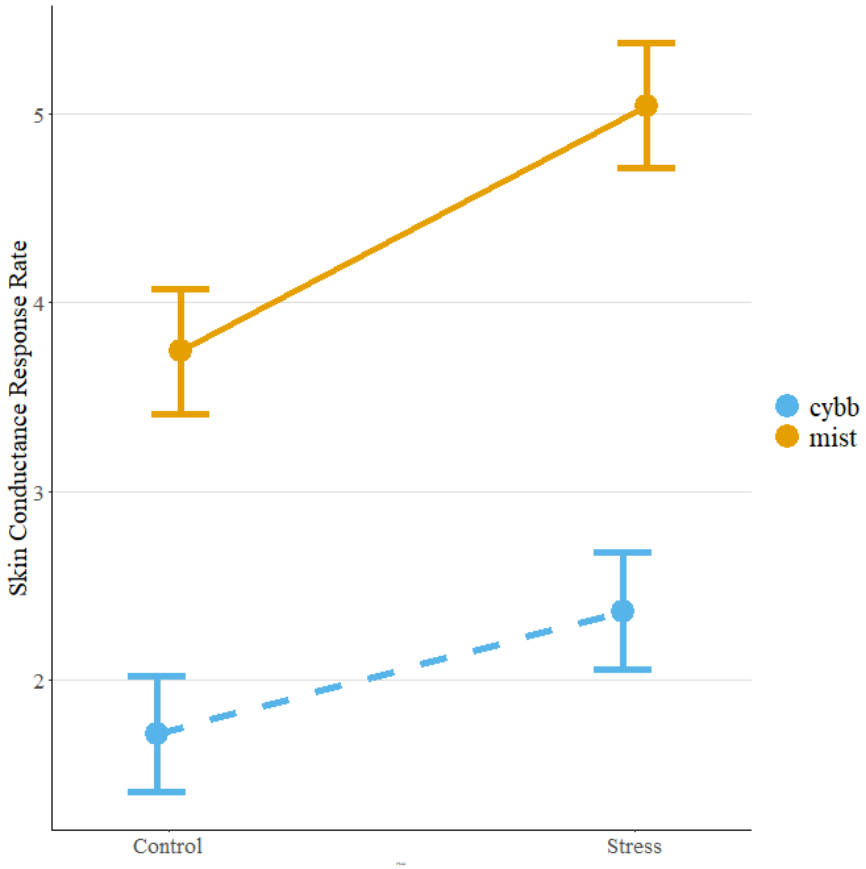

Figure 4: Visualization of the estimated marginal means (EMMs) for the Skin Conductance Response Rate (SCRR). **Note:** The error bars show the standard error of the means (SEMs).

3.3. EEG data

Only significant results are discussed in this section; the interested reader can find all EEG results, regardless of significance, on OSF (link:https://osf.io/tpm8u).

3.3.1. Power

3.3.1.1. Analysis of main effects

No significant main effects were found in the alpha frequency range (uncorrected *p's* > 0.05; corrected *p's* > 0.26). In the beta frequency range, one result was significant before multiple comparison correction, an increase in the left orbitofrontal cortex (β = 0.01; *SE* = 0.004; *t* = 2.62; *p* = 0.009; *d* = 0.35; *CI* = [0.08,0.6]), but this did not remain significant after correction (*p* = 0.094). Given the statistical insignificance, no figures are presented in the article, but these can be found in supplemental materials (section 6.5.4.).

3.3.1.2. Analysis of interaction effects

Within the alpha frequency range, no significant interaction effects were found (*p's* > 0.8). Two significant interaction results were found in the beta frequency range before multiple comparison correction, relating to the left frontal region and the left temporal region (*p's* < 0.02). But these results were insignificant after multiple comparison correction (*p's* > 0.05). Further analysis of the individual contrasts indicated that for both interactions, a significant increase in beta power in the Cyberball paradigm (left frontal region: β = 0.02; *SE* = 0.007; *t* = 2.48; *p* = 0.01; *d* = 0.44; *CI* = [0.09, 0.8] & left temporal region: β = 0.017; *SE* = 0.008; *t* = 2.1; *p* = 0.04; *d* = 0.37; *CI* = [0.02, 0.73]) was present while beta power did decrease, although not significantly, during the MIST paradigm (*p's* > 0.13). Given the statistical insignificance, no figures are reported, but these can be found in the supplemental materials (section 6.5.5.).

3.3.1.3. Exploratory analysis

Within the alpha frequency range, no significant changes were found for the Cyberball paradigm, but for the MIST paradigm, power increased in both the left (β = 0.03; *SE* = 0.01; *t* = 2.86; *p* = 0.046; *d* = 0.57; *CI* = [0.18, 0.97]) and right (β = 0.028; *SE* = 0.01; *t* = 2.69; *p* = 0.047; *d* = 0.52; *CI* = [0.13, 0.92]) precuneus/PCC complex. Within the beta frequency range, power increased in the left orbitofrontal region (β = 0.016; *SE* = 0.005; *t* = 3.11; *p* = 0.02; *d* = 0.55; *CI* = [0.19, 0.92]), left frontal region (β = 0.018; *SE* = 0.006; *t* = 2.94; *p* = 0.02; *d* = 0.52; *CI* = [0.16, 0.89]), left temporal (β = 0.017; *SE* = 0.0006; *t* = 2.66; *p* = 0.02; *d* = 0.47; *CI* = [0.11, 0.84]) and right temporal (β = 0.018; *SE* = 0.007; *t* = 2.75; *p* = 0.02; *d* = 0.49; *CI* = [0.13,

0.85]) regions during the Cyberball paradigm, while no changes were identified in the MIST paradigm.

3.3.2. Functional connectivity

3.3.2.1. Analysis of main effects

Based on the results of EEG power data, connections involving the left orbitofrontal cortex in the beta frequency range will be considered, resulting in 9 connections. No significant results were found either before (*p's* > 0.06) or after (*p's* > 0.32) multiple comparison corrections.

3.3.2.2. Analysis of interaction effects

Based on the results of the EEG power data, connections involving the left frontal or left temporal regions in the beta frequency range are considered, resulting in 17 connections. No significant result was found before (*p's* > 0.06) or after multiple comparison corrections (*p's* > 0.9).

3.3.2.3. Exploratory analysis

No significant results were found for either the Cyberball (*p's* > 0.59) or the MIST (*p's* > 0.31) paradigms.

4. Discussion and conclusion

Given the severe consequences on mental and physical health when an individual lacks positive social interactions or is exposed to aversive social environments (J. T. Cacioppo & Cacioppo, 2014; McLaughlin et al., 2019; Orben et al., 2020; Umberson & Karas Montez, 2010), understanding how the brain recognizes and responds to possible social threats, i.e. *psychosocial stressors*, is a longstanding, evolving research question in the field of psychology and psychiatry (Lazarus, 1993, 2000, 2006). This investigation, whereby the neuronal stress response is induced through a variety of paradigms employing different psychosocial stressors and subsequently measured, mainly with fMRI, resulted in the identification of several recruited cortical and subcortical regions (Berretz et al., 2021; S. Cacioppo et al., 2013; Dedovic et al., 2009; Muscatell et al., 2021; Mwilambwe-Tshilobo & Spreng, 2021; van Oort et al., 2017; J. Wang et al., 2018). These regions show relatively consistent (de)activation patterns when results are compared according to the employed stressor and/or paradigm (e.g., Cacioppo et al., 2013; Wang et al., 2017), but when studies employing multiple paradigms and stressors are examined together, surprisingly little convergent neuronal activity can be identified (Berretz et al., 2021; van Oort et al., 2017). Possible reasons for this could be the fact that fMRI, while having a high spatial resolution, measures neural activity indirectly, thus potentially missing aspects of the neural stress response, or that different psychosocial stressors evoke highly distinct neural responses.

Therefore, in the current study, we set out to investigate whether similar or divergent neural activity in brain regions commonly involved in the psychosocial stress response (i.e., the anterior insula, the precuneus/PCC complex, orbitofrontal region, lateral frontal region, and temporal region) can be detected by means of EEG. In order to do this, we exposed a large sample of healthy, adult participants to two commonly employed psychosocial stressors, social-evaluative threat (SET) and ostracism using the MIST and Cyberball paradigms respectively, in a within-subjects design. In order to compare the stress response as best as possible across both paradigms, the recovery phase of the stress response was analyzed by evaluating the resting-state EEG data collected directly after stressor exposure and comparing the obtained results with the direct recovery of an active control condition. We furthermore collected both physiological and self-report data to further gain insight into the full bodily psychosocial stress response during the stressors.

Results from the self-report questionnaires show that for both paradigms, negative affect (NA) increased after stress exposure, compared to the active control condition (p's < 0.01). This result aligns with our hypothesis and reconfirms the common notion that individuals experience stressful conditions as negative (Beekman et al., 2016; Ordaz & Luna, 2012). Our hypothesis regarding self-reported stress, however, was only partly confirmed. In the MIST paradigm, self-reported stress did increase significantly, but this increase was not identified in the Cyberball paradigm. The physiological results regarding the SCRR showed a similar pattern, where a significant increase for the MIST paradigm was identified, and no significant changes in the Cyberball paradigm were found. The RMSSD results, however, did not show a significant change for either the Cyberball or the MIST. The latter result aligns with our hypothesis regarding the Cyberball, as no elevated physiological effects (i.e., cortisol levels) have previously been identified (Helpman et al., 2017; Zöller et al., 2010), but contradicts our hypothesis regarding the MIST. Multiple causes are possible for this: it is possible that while the MIST stress condition was experienced as stressful at the end (when the questionnaire data was collected), it was not experienced as such continuously; the fixed order of conditions however could also be the reason for the insignificance. Nevertheless, taking the self-report and physiological data together, it becomes clear that different psychophysiological reactions are evoked by each paradigm. While the MIST results in a stress response that is measurable on both the physiological and psychological level (consistent with previous research; Dedovic et al., 2005), the Cyberball seems not capable of eliciting any (measurable) physiological effect, and participants do not seem to consider the exclusion phase more stressful as compared to the inclusion phase.

Results of the EEG power values regarding the possible main effects, whereby the influence of psychosocial stress regardless of the specific employed stressor is investigated, indicate no significant changes in either the alpha or beta frequency range. It should be noted however that a main effect in the beta range for the left orbitofrontal region was identified before MCC, where beta power increased. Our hypothesis regarding the main effect of the bilateral anterior insulae, where we expected an increase in both regions, has thus not been confirmed. Results regarding interaction effects, investigating whether brain regions exhibit distinct power changes across the two stressors, show a similar pattern compared to the main effects: nothing significant has been found after MCC, contradicting our hypothesis regarding the precuneus/PCC complex. Similarly, however, in the beta band, two regions exhibited significant effects (before MCC), the left frontal and left temporal regions. This lack of results

shows that no (investigated) region exhibits clearly similar or distinct power changes across psychosocial stressors.

Results from the exploratory analysis, investigating the Cyberball and MIST separately, are more promising. After MCC, four regions showed significantly increased power in the beta range in the Cyberball paradigm: the left orbitofrontal region, left frontal region, and left and right temporal region. Increased activity of the left orbitofrontal cortex is in line with previous literature, wherein the left inferior orbitofrontal cortex exhibits consistent increased activation when participants are exposed to the Cyberball (S. Cacioppo et al., 2013; Mwilambwe-Tshilobo & Spreng, 2021; Vijayakumar et al., 2017). This activation likely reflects the engagement of social-cognitive processes, given that the left orbitofrontal cortex is also found when other paradigms investigating social and evaluative processes related to oneself are employed (Burnett et al., 2011; Pfeifer et al., 2011, 2013), and disruptions in social behavior have consistently been observed in patients with damage to the orbitofrontal regions (Bechara et al., 2000). Increased activity in the middle and superior frontal gyrus (the regions included in the "frontal region" in this article) has also been identified in the Cyberball paradigm (Berretz et al., 2021). These regions have been linked with neuronal processes related to emotion regulation, which is especially important during the recovery phase of the stress response (Crowell et al., 2013; Ochsner & Gross, 2005; Torre & Lieberman, 2018) and are hypothesized to play an important role in the regulation of amygdala functioning, highlighting its possible function as a controlling agent of neural affective responses from the amygdala (Torrisi et al., 2013). Of note here is the fact that increased activity is also often identified in the right frontal regions, which is not found in the current study. It is possible that technical limitations (see below) might be the cause for this absence. Finally, increased left and right temporal gyri (mostly middle and superior) activity has also been found in previous literature regarding the Cyberball paradigm (Wang et al., 2017) and are believed to be linked to emotional cognition and reappraisal (Blair et al., 2007; Ochsner et al., 2004). Taken together, neural recovery from ostracism, induced through the Cyberball paradigm, results in increased activity in several brain regions linked with social, cognitive, and emotion regulatory processes.

Results from the exploratory analysis regarding the MIST paradigm identify two brain regions that changed significantly, the bilateral precuneus/PCC complex. Within the alpha frequency range, both regions showed a significant increase. Alpha power increases in the bilateral precuneus/PCC complex, given the view of alpha oscillations representing neural inhibition mechanisms (Jensen & Mazaheri, 2010; Mathewson et al., 2011), likely reflect a

decreased cortical activity within this region, which aligns with previous results from both fMRI (Berretz et al., 2021; Fliessbach et al., 2007; Lindner et al., 2015; Sánchez-García et al., 2021) and EEG research (Vanhollebeke, Kappen, et al., 2023). The precuneus/PCC complex is mostly recognized as an important region of the default mode network (DMN), a "task-negative" network most active when external stimuli are not present and believed to represent self-reflective thoughts (Fransson & Marrelec, 2008). This interpretation is further solidified given that multiple studies have found increased activity within the complex during self-reflective-inducing tasks (Johnson et al., 2002; Lou et al., 2004), and aligns with the model of Cavana and colleagues (2006) where precuneus/PCC activity has a positive relation with the degree of internal focus (Cavanna & Trimble, 2006). The relationship between precuneus/PCC activity and stress has also been investigated, and an inverse relationship between the activity of the complex and the degree of stress was identified (Guendelman et al., 2022; Pires et al., 2018). Considering both aspects, our results thus imply that during the recovery from SET, induced through the MIST paradigm, individuals are more externally focused, which might be linked with the regulation of possible external threats (Cabanis et al., 2013; Cavanna & Trimble, 2006; Leech & Sharp, 2014).

Considering all results together, a somewhat surprising conclusion is reached. When each paradigm is analyzed in isolation, several brain regions exhibit changes consistent with previous literature, where the exclusion phase of the Cyberball elicited increased power in the beta band of the left orbital and frontal region, and both the left and right temporal region. The MIST resulted in increased alpha power of the left and right precuneus/PCC complex. When data from both paradigms is combined, however, no significant result is found. The absence of clear similar or dissimilar neural activity somewhat aligns with previous fMRI studies, as only increased bilateral anterior insula activity and decreased right amygdala activity was identified (Berretz et al., 2021), and thus shows the highly divergent neural stress responses evoked by different paradigms. It might be possible that these differences are due to the different emotion regulation strategies that are employed during the recovery phase given the different social threats that are employed by each paradigm. The insula and amygdala have been identified as key regions involved in emotion regulation, possibly explaining their presence in the aforementioned meta-analysis (Berretz et al., 2021; Etkin et al., 2015). The results of our explorative analysis largely align with this explanation, as both increased activity of frontal and temporal regions as well as decreased precuneus/PCC activity have been linked with different regulation strategies (Messina et al., 2021).

Other aspects and potential limitations should also be considered, however. From a methodological point of view, the main limitation is the selection of brain regions and analysis choices. Although this selection was done based on several reviews and meta-analyses, it is still possible that other regions aside from those investigated in the current study do display the behavior we set out to find. Additionally, while amplitude envelope correlation has been identified as a reliable measure of functional connectivity (Colclough et al., 2016), other FC measures might have uncovered neural communication that is not captured using AEC. From a technological point of view, the main limitation is the absence of individual MRI scans which, given that small morphological head differences between participants lead to errors in the precise localization of neuronal activity in the source space, decreases the spatial resolution of the obtained source reconstructions, (Céspedes-Villar et al., 2020). The usage of atlases probably complicates this issue further, as brain regions defined by the atlas likely do not overlap completely with the individual anatomy of a participant or the previously identified regions in the systematic reviews and meta-analyses. This technical limitation is possibly the reason that no main effect for the anterior insulae was found as the identified bilateral clusters by Berretz and colleagues (2021) are small, making it possible that the spatial resolution of EEG is insufficient to consistently separate their activity from that of neighboring regions due to the activity spread introduced by the ESI method (Song et al., 2015; Stenroos & Hauk, 2013).

The final, theoretical aspect is perhaps the most important of all and refers to the implicit assumption that the employed psychosocial stressors in the current study are in fact stressors. Given our results, however, this assumption might be challenged when we consider the results with regard to ostracism, as incorporated by the Cyberball paradigm. While the Cyberball was successful at inducing NA, participants did not find the exclusion phase more stressful compared to the inclusion phase. Similarly, no significant physiological changes were identified, while these were present during the stress phase of the MIST paradigm. While limitations of the current study (i.e., specific implementation of the Cyberball paradigm, fixed order of inclusion before exclusion condition, only one question regarding the experienced stress) might be the reason for the absence of physiological or self-report indications of stress induction and should thus be considered when interpreting the results, we propose another explanation that might be better suited for these (and in extension, previous) results: ostracism, as it is conveyed in the EEG-compatible Cyberball paradigm, should not be considered an acute psychosocial stressor. The most likely reasons for this are the adaptations made to the original Cyberball paradigm (Williams et al., 2000) such as the increased amount of throws and

consequently increased duration in each condition or the usage of a within, rather than a between-subjects design (Hartgerink et al., 2015; Vanhollebeke, Aers, et al., 2023). It should be mentioned however that previous studies investigating cortisol responses to the Cyberball that identified no significant changes employed the original paradigm (Helpman et al., 2017; Zöller et al., 2010), but given the limited studies our conclusion should only be considered with regard to the EEG-compatible version.

In conclusion, the comparison of neural responses across the Cyberball and MIST paradigms shows that no region exhibits clear uniform or distinct activity changes, while the analysis of each paradigm separately shows activity changes in several regions that are consistent with previous literature. Possible reasons for this could be that different emotion regulation and coping styles are employed during the recovery of each paradigm that rely on largely the same neural regions, yet recruit these regions somewhat differently due to the specific psychosocial threat present in each paradigm. The inherent limited spatial resolution of EEG (especially when no individual MRI scans are available) should also be considered, as it might hinder the capability to consistently identify neural activity of specific regions in source space. Other results aside from EEG however, hint at the fact that the Cyberball, a common paradigm for the investigation of ostracism which is believed to be a psychosocial stressor (Muscatell et al., 2021), might not be able to evoke a stress response. Although the Cyberball is the most commonly employed paradigm for the investigation of ostracism and has a significant impact on the mental state of an individual (Hartgerink et al., 2015), the assumption that this experience is stressful might be incorrect. We therefore advise future research to re-evaluate the Cyberball as a psychosocial stressor as its neural, physiological, and behavioral effects question its alignment with other stressors and accompanying paradigms.

5. References

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6. Supplemental information

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6.3. Declaration of competing interest

All authors report no financial interests or potential conflicts of interest related to this publication.

6.4. Open practices statement

All data is available on OSF (link: https://osf.io/t28rn/). Code is available on OSF (link: https://osf.io/pa8ed/) and Github (link: https://github.com/dx2r/PhD_EEG_ Pipeline).

6.5. Supplemental materials

6.5.1. In- and exclusion criteria

General criteria

- Born before 1977
- Born after 2003
- Current pregnancy
- Current depressive episode
- (History of) other pyschiatric disorders
- Current abuse addiction (nicotine/caffeine not considered)
- Eye disease (usage of glasses not considered)
- Heart or respiratory problems
- Participated in an earlier study (https://doi.org/10.1038/s41598-023-35808-y)
- Psychology students

EEG-related criteria

- Personal or family history of epilepsy
- Recent neurosurgical procedures
- Inner ear prosthesis
- Metal/magnetic objects in the brain or around the head that cannot easily be removed
- Skin condition on the head
- Current use of psychotropic medication
- Neurological problems
- Dreadlocks
- Tightly curled hair

6.5.2. Standard settings for brainStorm

- SimNIBS settings
    - Vertex density : 0.5
    - Number of vertices on the CAT12 cortex surface : 15000
- DUNEURO settings
    - Source space : cortex surface
    - Forward modeling methods : DUNEuro FEM
    - FEM layers & conductivities
        - White matter : 0.14
        - Gray matter : 0.33
        - Cerebrospinal fluid : 1.79
        - Skull : 0.008
        - Scalp : 0.43
    - FEM solver type : Continuous Galerkin
    - FEM source model : Venant
    - Vennant options
        - Number of moments : 3
        - Reference length : 20
        - Weighting exponent : 1
        - Relaxation factor exponent : 6
        - Mixed moments : on
        - Restrict : on
    - Source space
        - Shrink source space : 0 mm
        - Force source space inside layer ‘gray’ : on
- Compute sources settings
    - Method : minimum norm imaging
    - Measure : current density map
    - Source model dipole orientations : constrained – normal to cortex
    - Depth weighting
        - Order : 0.5
        - Maximal amount : 10
    - Noise covariance regularization
        - Diagonal noise covariance
    - Regularization parameter
        - Signal-to-noise-ratio : 3.00
    - Output mode : inverse kernel only

6.5.3. Supplemental figure – RMSSD result

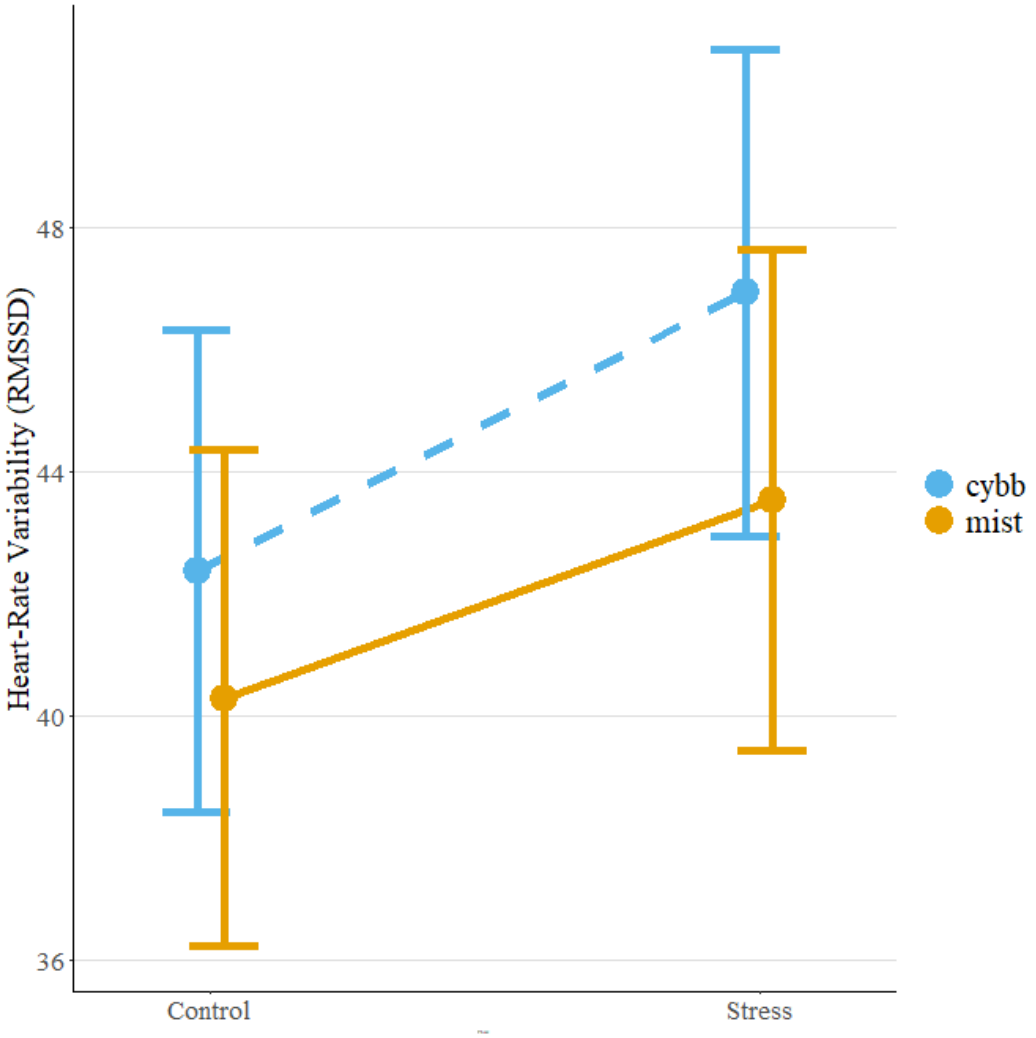

Figure (extra): Visualization of the estimated marginal means (EMMs) for the Root Mean Square of Successive Differences (RMSSD) between heartbeats . **Note:** The error bars show the standard error of the means (SEMs).

6.5.4. Supplemental figure – EEG relative power main effect of the left orbitofrontal region

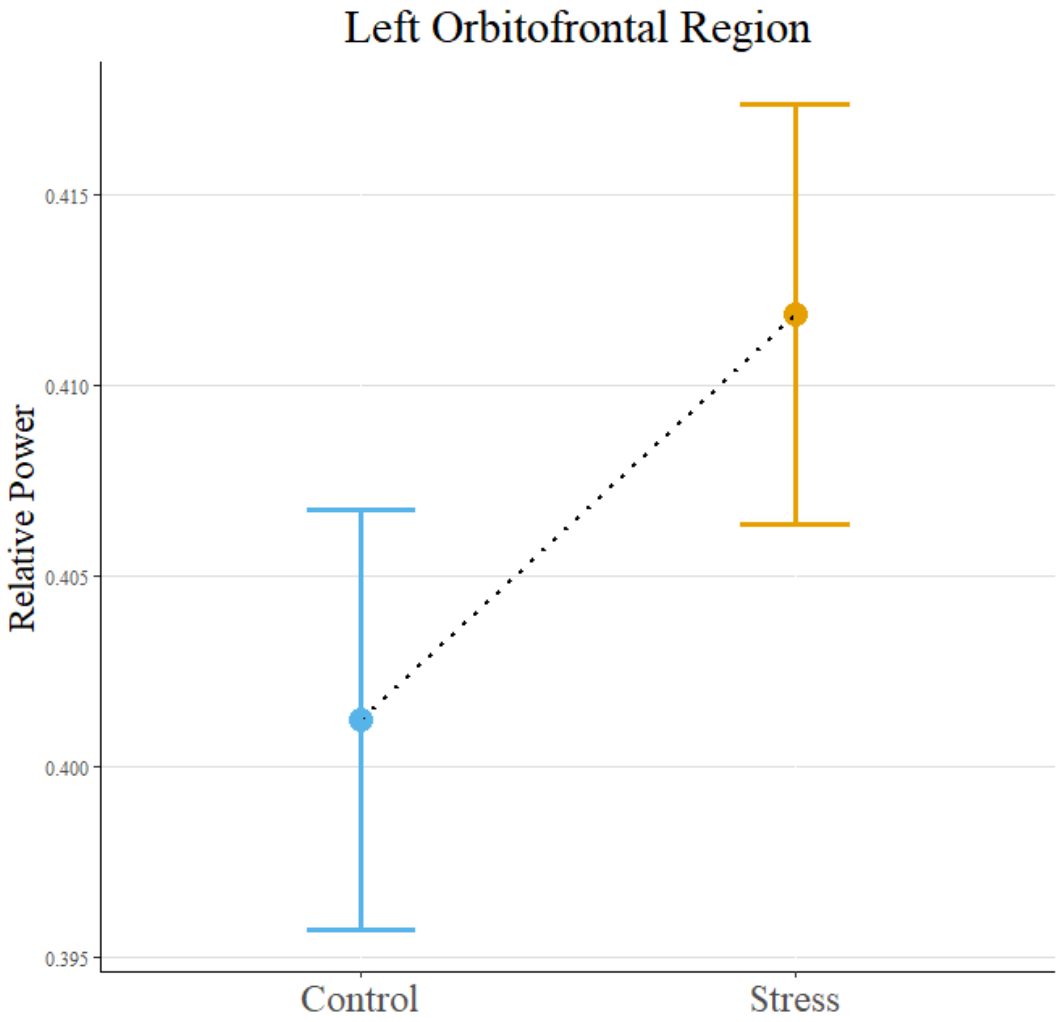

Figure (extra): Visualization of the estimated marginal means (EMMs) for the EEG relative power main effect of the left orbitofrontal region . **Note:** The error bars show the standard error of the means (SEMs).

6.5.5. Supplemental figures – EEG interaction effects

6.5.5.1. EEG relative power interaction effect of the left frontal region

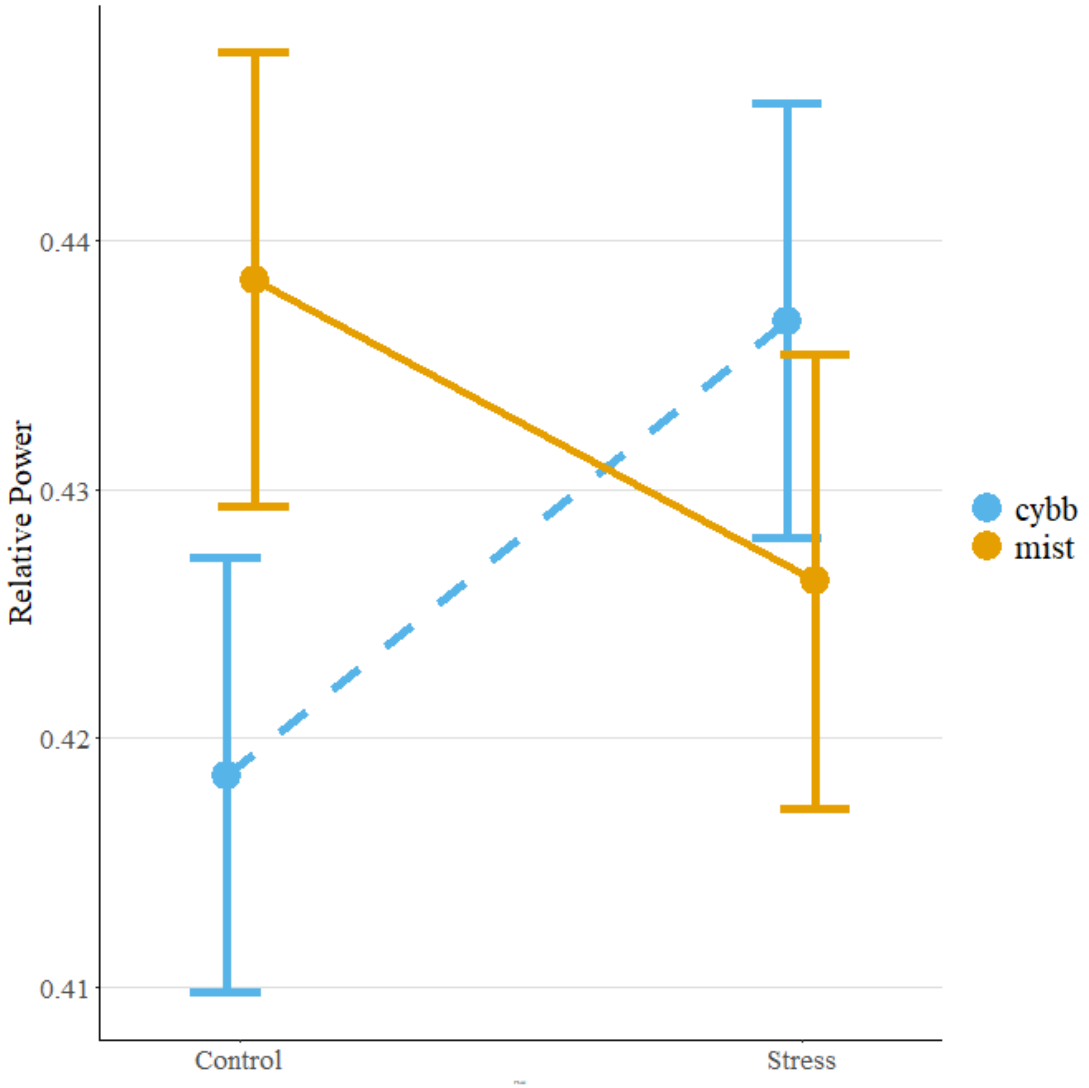

Figure (extra): Visualization of the estimated marginal means (EMMs) for the EEG relative power interaction effect of the left frontal region . **Note:** The error bars show the standard error of the means (SEMs).

6.5.5.2. EEG relative power interaction effect of the left temporal region

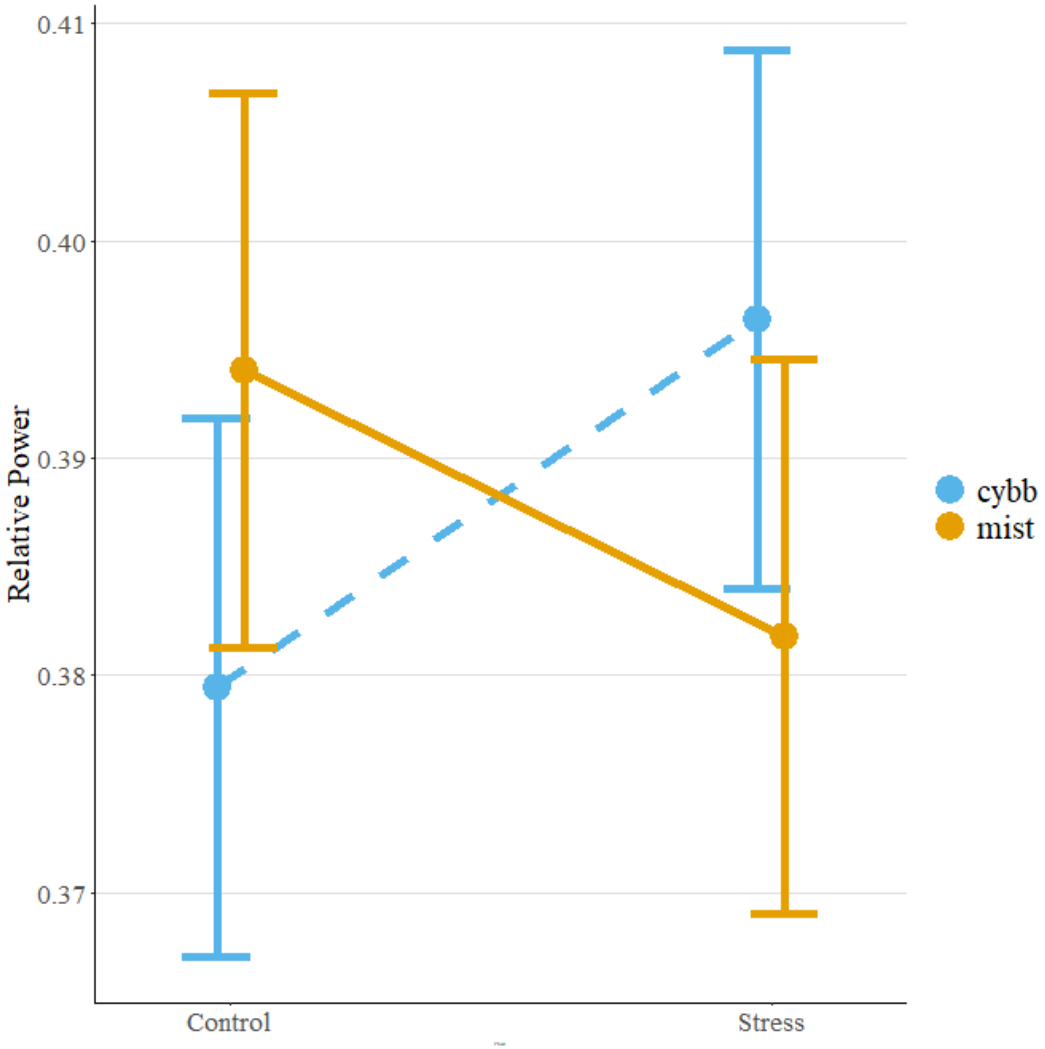

Figure (extra): Visualization of the estimated marginal means (EMMs) for the EEG relative power interaction effect of the left temporal region . **Note:** The error bars show the standard error of the means (SEMs).

Chapter 6

General Discussion

Encountering stressful moments is a daily experience for almost any individual. Ranging from small instances of stress arising from daily hassles to significant emotional events, stress occurs commonly throughout life (Epel et al., 2018). When the individual is exposed to a potentially stressful stimulus (i.e., a *stressor*), a bodily reaction is set into motion that aims to adapt to the threat or overcome the stressor, called the *stress response* (Epel et al., 2018; Lazarus & Folkman, 1984). The stress response is initiated and coordinated by the brain, which adjusts various biological systems in the body (e.g., the immune, respiratory, or cardiac system) through mainly two effector systems: the sympathetic-adreno-medullar (SAM) and hypothalamus-pituitary-adrenal (HPA) axes (Epel et al., 2018; Godoy et al., 2018; Kudielka, Schommer, et al., 2004; McEwen, 2007). The immediate reaction, often called the "fight-or-flight" response, is mostly orchestrated by the SAM axis and results in several adaptations in the body, ranging from increased breathing and heart rate to more alertness to the environment (McEwen, 2007). The HPA axis evokes a slower response aimed at further coordinating the stress response as well as reversing the initiated bodily changes to their baseline condition to prevent lasting damaging effects (Godoy et al., 2018).

The stress response is an *adaptive* response under normal circumstances but can become harmful if stressors are either too severe (traumatic events; Yehuda et al., 1998) or too common and enduring (chronic stress; Gottlieb, 2013). Under these circumstances stress can have devastating effects on the mental and physical health of an individual. Researchers have investigated these effects, and have found links between stress and nine out of the ten most common causes of mortality (Kappen et al., 2023) and have further identified stress as an important factor in the development and progression of several mental disorders such as depression (Blackburn-Munro & Blackburn-Munro, 2001; Breslau & Davis, 1986; Briley & Lépine, 2011; Checkley, 1996; Ferrari et al., 2013; Liu et al., 2020; Tafet & Bernardini, 2003), anxiety disorder (Dieleman et al., 2015; Patriquin & Mathew, 2017; Pêgo et al., 2009), post-traumatic stress disorder (Sherin & Nemeroff, 2011; Yehuda et al., 2015) and schizophrenia (Corcoran et al., 2003; Walker & Diforio, 1997).

Considering the severe physical and mental consequences of maladaptive forms of stress, significant efforts have been made to better understand which stimuli evoke stress responses. One specific set of stimuli called *psychosocial stressors*, defined as stimuli arising from social interactions and situations that are novel, unpredictable, or uncontrollable (Epel et al., 2018; Koolhaas et al., 2011; Vanhollebeke et al., 2022), has been recognized as having a significant influence on the subsequent health of an individual (Backé et al., 2012; Greenwood

et al., 1996; Kemeny & Schedlowski, 2007; Kudielka, Schommer, et al., 2004; McEwen & Seeman, 1999). Two key reasons have been proposed for their prominence in the stress-disease link: they are ubiquitous (DeLongis et al., 1982; Williams, 2007) and threaten several core needs of the individual (Baumeister et al., 2007; Baumeister & Leary, 1995; Williams, 2009).

As the central organ of the stress response, unraveling how the brain reacts to psychosocial stressors has been a major focus of psychosocial stress research (McEwen, 2009; Muscatell et al., 2021). Investigating the neural psychosocial stress response is most commonly done with *functional magnetic resonance imaging* (fMRI) and has resulted in the identification of several brain regions such as the anterior insula, inferior frontal gyrus, amygdala, hippocampus, hypothalamus, precuneus, anterior and posterior cingulate cortex (ACC/PCC), and parts of the temporal and prefrontal lobe that all seem to play an important role in both processing the stressors as well as guiding the subsequent stress response (Berretz et al., 2021; Cacioppo et al., 2013; Dedovic et al., 2009; Kogler et al., 2015; Mwilambwe-Tshilobo & Spreng, 2021; Wang et al., 2017). Research into how these regions communicate and how psychosocial stress influences this communication has identified the amygdala as a key region of the psychosocial stress response (Godoy et al., 2018; McEwen et al., 2016; Thayer & Lane, 2009). Additionally, it has been shown that many of the aforementioned regions are part of either the salience, central executive, or default mode network that together form the triple network model wherein dysfunctions have been linked to multiple psychiatric disorders (Menon, 2011; van Oort et al., 2017). Other research lines have further investigated the interactions between the prefrontal cortex, amygdala, and hippocampus (McEwen et al., 2016) and show that disruptions in these functional connections due to repeated stress exposure might give rise to the damaging effects of stress as the initiated stress responses are not controlled adequately by the prefrontal cortex anymore (Danese & McEwen, 2012; McEwen & Seeman, 1999; Park et al., 2018; VanTieghem & Tottenham, 2018).

Taken together, substantial knowledge regarding the neural psychosocial stress response has been gained through the usage of fMRI. The indirect measure of neural activity on which the neuroimaging technique relies (the BOLD response), however, limits our understanding as results are often interpreted as "increased" or "decreased" activity of regions, while the underlying neural mechanisms are more complex (Heeger & Ress, 2002; Logothetis, 2008). fMRI additionally has low temporal resolution, which possibly further restricts the ability of this neuroimaging technique to unravel the dynamic processes in the brain as it reacts to psychosocial stressors and guides the subsequent stress response.

Electroencephalography (EEG) has the potential to overcome the aforementioned limitations of fMRI. Although it has a lower spatial resolution than fMRI, the direct assessment of neural activity at a much higher temporal resolution opens additional avenues of research into aspects of neural activity that cannot be captured by fMRI (Cohen, 2014, 2017). The potential of EEG is significant, but EEG research endeavours into the psychosocial stress response that have employed EEG have been restricted to the direct analysis of the data captured by the electrodes, called *sensor level* analyses. These analyses are limited in their potential contribution to the collective understanding of the stress response as they cannot easily be compared with fMRI results, resulting in a gap between both research fields. This hindrance can be addressed with *electrical source imaging* (ESI), the mathematical process by which the most likely source distributions in the brain that caused the measured sensor level EEG data are estimated (Michel & Brunet, 2019). This allows translating the data captured at the scalp into activity patterns of the brain. ESI makes it possible to investigate neural activity of specific regions of interest (ROIs) in the brain, and is thus capable of bridging the present gap between EEG and fMRI research into the neural psychosocial stress response.

The aims of this dissertation were twofold. Firstly, the EEG-psychosocial stress research field was critically evaluated and reviewed. Secondly, the possible added value of ESI was assessed. This was done by initially comparing the sensitivity of source level EEG measures with commonly employed sensor level measures when only a psychosocial stressor is present. Subsequently source level EEG measures, reflective of the neural activity patterns of several commonly identified ROIs in the psychosocial stress response, were evaluated by identifying possible similar or divergent changes during the recovery phase of the stress response, induced by two different psychosocial stressor paradigms, the Cyberball (Williams et al., 2000) and Montreal Imaging Stress Task (MIST; Dedovic et al., 2005).

In the following sections, the main findings of the presented studies in this dissertation will be presented and discussed within the larger scope of the research field. Additionally, the main findings of the experimental studies specifically (chapters 4 and 5) will be discussed in relation to other studies that employ EEG and fMRI to investigate psychosocial stress. Subsequently, the limitations of the presented studies will be discussed followed by suggestions for future studies. Finally, the general conclusions of the dissertation are presented.

1. General overview of the findings

The first study, presented in **chapter 2**, provides results from a systematic review of the studies that employed spectral EEG analyses for the investigation of the psychosocial stress response (Vanhollebeke et al., 2022). Firstly, the main definition of psychosocial stress that is employed throughout this dissertation was defined (i.e., *" Psychosocial stress is a particular relationship between the person and the social environment that is appraised by the person as taxing or exceeding their resources and endangering their well-being"* ; Lazarus & Folkman, 1984) and psychosocial stressors were defined as *" threatening or stressful stimuli arising from social interactions due to the novel, unpredictable or uncontrollable characteristics"*. Next, the three phases of the stress response were delineated. The *anticipatory phase* was defined as the time between the moment an individual becomes aware of an upcoming stressor, and the presence of said stressor. The *reactive phase* was defined as the time that the individual is exposed to the stressor directly. The *recovery phase* was defined as the time after stressor exposure when the initiated stress response wanes and the evoked physical and mental alterations return to their normal, baseline levels. Finally, a restriction on the included literature was imposed by limiting the studies to those that investigate the psychosocial stress response through the usage of *acute* (i.e., short term), *laboratory* (i.e., conducted in a controlled environment) psychosocial stressors.

Results from this review highlighted the prominence of spectral power as an analysis tool for the investigation of acute laboratory psychosocial stressors. Spectral power in the alpha and beta power, mostly computed from frontal electrodes, as well as frontal alpha asymmetry (FAA), an alpha power-derived EEG measure, were most commonly employed. Alpha power decreased consistently in all phases of the stress response which was confirmed through a meta-analysis that identified a moderate effect size across studies (Hedge's $g = 0.6$). Beta power showed a tendency to increase in both the reactive and recovery phase (no data on the anticipatory phase was present), but a meta-analysis of this measure showed that this increase was insignificant. FAA, obtained by log transforming the alpha power data from two frontal electrodes (either F3 and F4 or F7 and F8) and subtracting one from the other, is assumed to reflect relative differences between the left and right frontal lobe (Smith et al., 2017). Two meta-analyses were conducted for this measure (for each electrode pair previously mentioned), but neither indicated a consistent change across stress phases. The absence of significant results for this measure across studies, while individual studies reported significant changes, could possible be explained by the right-shift model proposed by Ocklenburg and colleagues (2016).

In their model, Ocklenburg stated that psychosocial stress results in increased activity of mainly the right hemisphere, but that the final obtained FAA value is largely dependent on co-occurring cognitive processes in frontal regions (Ocklenburg et al., 2016). Of importance here is that this model already points to one possible limitation of the current research field of psychosocial stress, the co-occurence of non-psychosocial stressors. Outside of these three main measures, a multitude of other methods (e.g., delta, theta, sigma, and gamma power, alpha attenuation coefficient AAC, slowing ratio, relative gamma, coherence, phase-amplitude coupling) have been employed, but to a far lesser extent and with greater variety in their results across stress phases (Vanhollebeke et al., 2022).

Considering the experimental work presented in chapter 4 and 5, additional conclusions can be inferred from chapter 2. First and foremost is the absence of electrical source imaging (ESI) in the EEG-psychosocial stress research. Of the 34 included studies, none employed ESI thus all results were limited to the sensor space. Keeping the effects of volume conduction in mind, these results should be interpreted with caution (Schaworonkow & Nikulin, 2022). This is especially important regarding FAA, as this measure is assumed to reflect laterality differences in neural activity of the (pre)frontal lobes (Smith et al., 2017). Given that FAA did not show consistent changes in this chapter and a similar conclusion was obtained for this measure as a biomarker of depression (van der Vinne et al., 2017), it was not further explored in chapters 4 and 5. The absence of ESI results additionally makes it difficult to connect the body of spectral EEG studies with the multitude of fMRI results, and therefore somewhat limits the extent to which these studies can contribute to the collective understanding of the neural psychosocial stress response. Of importance to note here is that this conclusion does not diminish the scientific value of these studies, it just highlights the possible added value that ESI can bring to the research field as it can bridge both research lines.

Aside from the absence of ESI, functional connectivity (FC) was also not commonly conducted, as only three out of the 34 studies employed this analysis method (Vanhollebeke et al., 2022). This result was surprising, as EEG, together with MEG and fNIRS, is an excellent neuroimaging technique for functional connectivity analyses given its high temporal resolution. Contrary to fMRI, where the most commonly employed FC measure is correlation, EEG can be analyzed using a multitude of FC methods (Bastos & Schoffelen, 2016; Sakkalis, 2011). Therefore, in chapters 4 and 5 amplitude envelope correlation (AEC) was used to further investigate how the brain reacts to acute psychosocial stressors given its robustness of over more insightful, but also more complex FC measures (Colclough et al., 2016).

Chapter 3 presented a second systematic review that focused on the Cyberball paradigm (see chapter 1, section 1.1.2.1.) and reviewed the event-related potential (ERP) results obtained during the paradigm from healthy, adult populations (Vanhollebeke, Aers, et al., 2023). The main objective of this chapter was to evaluate whether the ERP results reflect the activity of an ostracism-specific neural alarm system, or if they instead show more general neural mechanisms that might be evoked by other characteristics of the paradigm that are unrelated to the social context of ostracism. This question is not unique to the field of ERPs, but is a longstanding point of discussion in the field of ostracism research (Mwilambwe-Tshilobo & Spreng, 2021; Somerville et al., 2006).

Results from this review showed that 7 ERP components, the contingent negative variation (CNV), the P2, the N2 (divided into an early and late component), The P3a, the P3b, and the late positive potential (LPP), have been investigated in the Cyberball paradigm. Due to the limited amount of studies and individual differences regarding the specific conditions and throw types (i.e., throws from a confederate to the participant, called *receive* throws, and throws between the two confederates, called *neglect* throws) that were investigated, for most components no clear origin could be identified. For one component however, the P3b, a clear origin could be identified: *expectancy violations*; the idea that stimuli that are incongruent with the expectations of an individual evoke an aversive reaction that results in attempts to resolve the incongruency (Proulx et al., 2012). A string of studies spanning more than a decade, spearheaded by Professor Niedeggen, has evaluated the P3b in the Cyberball by both manipulating the classic setup of the paradigm (Weschke & Niedeggen, 2013, 2015, 2016) and evaluating ostracism in both healthy controls as well as individuals with borderline personality disorder (BPD) and social anxiety disorder (SAD) (Gutz et al., 2015; Weinbrecht et al., 2018, 2021). The results of this research led to the conclusion that the P3b results are most likely reflecting the processing of a neural system that detects expectancy violations. Moreover, it was shown that this neural system is not specific to ostracizing stimuli (Vanhollebeke, Aers, et al., 2023).

The results of this chapter can be considered sober (clearly stated in the concluding paragraph, see chapter 3, section 4.6.) as only a clear conclusion could be obtained for one of the seven investigated ERP components (Vanhollebeke, Aers, et al., 2023). It, however, provides insights that are vital for the interpretation and evaluation of the experimental studies in chapters 4 and 5, as well as the research field in general.

Most important is the danger of *reverse inference*, the invalid deduction that activity of a specific neural mechanism measured with neuroimaging methods (in this case, changes in ERP components measured with EEG) is proof that a specific cognitive function, linked with said specific activity in other scientific articles, is also present. This deduction is especially dangerous when the activation of the neural mechanism is not specific to the cognitive process (Poldrack, 2006). Considering that all ERP components reviewed in chapter 3 are not unique to the Cyberball but are identified across a multitude of experimental paradigms and conditions *in itself* already questions the assumption that these components are reflective of a specific neural alarm system (Brunia et al., 2011; Crowley & Colrain, 2004; Folstein & Van Petten, 2008; Hajcak et al., 2010; Polich, 2007). Considering reverse inference with regard to the general focus of this dissertation, it should be mentioned that it also sometimes occurs in stress research in general as it is sometimes employed for key regions of the psychosocial stress response. An important example of this is the amygdala, which is sometimes seen as the "fear center" of the brain and the instigator of the stress response (LeDoux, 1994). This representation is not necessarily incorrect, but the assumption that the amygdala are *only* involved in the stress response, however, is and has been addressed directly (Delplanque & Sander, 2021; Krueger, 2017). Therefore, the activity of the amygdala in itself should not be used as a validation for the presence or absence of stress in the individual. Returning to the studies in this dissertation, the interpretation of the results of chapters 4 and 5 should therefore be considered only within the paradigms that were employed, and no engagement of cognitive functions due to changes in the activity of ROIs can be assumed.

Aside from reverse inference, the importance of careful experimental design should be acknowledged. Many of the conclusions obtained in chapter 3 rely on minor adjustments to the paradigm display (e.g., Niedeggen et al., 2014, 2017; Weinbrecht et al., 2018, 2021), indicating the complexity and influence of the many aspects of the Cyberball. This consideration is most important for ERP studies, as the fundamental processes investigated in the short timeframe can be influenced by minute changes in the presentation of a paradigm, but it is also influential in EEG studies that employ spectral analyses (such as those in chapter 2) and evaluate longer segments of EEG signals. Limitations in the experimental design will therefore be discussed at length later in this chapter.

Finally, it should be mentioned that contrary to the other chapters, a rather direct conclusion has been obtained as to *how the brain evaluates* the stimuli presented in the Cyberball. Precisely due to the necessity of clearly defined stimuli and the short timeframe in

which the components are analyzed, which were seen as limitations in the introduction of chapter 2 as they limit the investigation of the psychosocial stress response to the reactive phase (Vanhollebeke et al., 2022), an explicit link between the stimuli and the evoked neural response can be established. This relation has subsequently led to the clear conceptualization of expectancy violations as an explanation for the observed P3b changes, a conclusion that is more explicit than those obtained in all other chapters.

Results from the first experimental study were presented in **chapter 4**, whose main objective was the evaluation of how psychosocial stressors in isolation affect EEG measures. In this study, a within-subjects design was employed whereby participants needed to solve a challenging cognitive task, Raven's matrices (Raven & Court, 1938), and received feedback after each individual matrix (Vanhollebeke, Kappen, et al., 2023). Depending on the condition (i.e., neutral or negative), the feedback presented either showed that the participant performed equally as well as a peer group (control condition), or performed gradually worse throughout the condition (negative condition). Our experimental design employed Raven's matrices that were comparable in complexity across both paradigms (i.e., no difference in task complexity), employed no differences regarding allowed time for each Raven's matrix (i.e., no additional time limit), and only adjusted the feedback after each matrix across conditions. Only the EEG data of the six-second feedback was subsequently analyzed for both conditions, thus isolating the psychosocial stressor of the paradigm, *social-evaluative threat* . Spectral theta, alpha, and beta power at frontal electrodes were assessed, as an earlier study had shown that the addition of social-evaluative threat to a cognitive task (the PASAT; Gronwall & Sampson, 1974) with a time limit did not elicit significant changes in these measures (Ehrhardt et al., 2021). Additionally, source level-derived spectral power in the theta, alpha, and beta range of the anterior insula (with parts of the inferior frontal gyrus), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus, and orbitofrontal cortex were also analyzed, and functional connectivity between regions that exhibited significant changes in power across conditions were also assessed using amplitude envelope correlation (AEC; Hipp et al., 2012). To evaluate the effectiveness of the experimental paradigm, self-assessment manikins (SAMs; a self-report questionnaire using pictures to assess the valence and arousal of an individual, see chapter 4, section 7.6.3.) and inter-beat interval (IBI) response analysis during the feedback was conducted (see chapter 1, section 2.1.2.).

The results of the SAM partly aligned with the hypothesis as valence decreased significantly. However, arousal also decreased significantly which contradicted the hypothesis. The IBI response analysis identified an increased heart rate acceleration during the negative feedback when compared to the control feedback, and shows the short-term increased sympathetic activity due to negative feedback and SET (Taelman et al., 2009; Vrijkotte et al., 2000; Ziegler, 2012). EEG sensor level results replicated the earlier findings of Ehrhardt and colleagues (2021), as no significant changes were identified for either theta, alpha or beta power at frontal electrodes. Subsequent Bayesian statistics further confirmed that the null hypothesis (i.e., no change across conditions) was more likely for all three measures. In source space, however, alpha power in the right PCC and precuneus, as well as the left precuneus increased significantly, and the functional connection between the left and right precuneus also increased in the alpha range (Vanhollebeke, Kappen, et al., 2023). All results clearly indicate that the precuneus/PCC complex shows increased alpha activity during short-term acute SET.

Two conclusions can be obtained from this chapter. Firstly, the measures alpha and beta power of frontal electrodes, identified as two of the most commonly employed measures to investigate psychosocial stress in chapter 2, do not change significantly due to psychosocial stress alone, but are more likely reflecting co-occurring cognitive processes (Ehrhardt et al., 2021; Vanhollebeke, Kappen, et al., 2023). This conclusion is nontrivial and points to a significant problem in the EEG-psychosocial stress research field. Secondly, the added value of ESI is highlighted in this study. Not only was it proven that source level-derived power measures were, contrary to sensor level-derived measures, sensitive enough to detect a purely psychosocial stress response, but these results can now be coupled back to the vast fMRI literature concerning psychosocial stress.

The results of the second experimental study were presented in **chapter 5**. Here the main objective was to evaluate whether the neural psychosocial stress response, induced by different paradigms, results in similar or dissimilar activity changes in several key regions. These regions were the anterior insula, orbitofrontal cortex, prefrontal region, temporal region, and PCC/precuneus complex. This study thus explores the possible influence of the specific stress induction paradigm on the subsequent neural stress response, as this influence has been noted in recent reviews and meta-analyses (Berretz et al., 2021; van Oort et al., 2017). A within-subjects design was employed where each participant first completed the Cyberball, and performed the MIST on a later day with at least seven days between each paradigm. To compare both stress responses optimally, resting-state EEG data captured directly after the control and

stress condition of each paradigm was analyzed, thus evaluating the *recovery phase* of the stress response (Vanhollebeke et al., 2022). Considering the results from chapter 4, no sensor level-derived measures were investigated. Spectral power in the alpha and beta bands were assessed for the aforementioned regions and functional connectivity between regions was evaluated using AEC. Similarly to chapter 4, self-report questionnaires assessing both negative affect and stress were employed that assessed negative affect and stress directly. These self-reports were analyzed directly after the control and stress conditions. Additionally, physiological data was collected during the control and stress conditions and analyzed to evaluate the effectiveness of the paradigms. ECG data was analyzed to obtain the RMSSD as a reflection of parasympathetic nervous activity (see chapter 1, section 2.1.2.), while EDA data was analyzed to compute the SCRR, thus evaluating sympathetic nervous activity (see chapter 1, section 2.1.1.).

Results from the self-report data indicated that the stress condition of both paradigms resulted in increased negative affect compared to the control condition. Participants rated the stress condition of the MIST as more stressful, but no significant change was identified in the Cyberball. SCRR was increased during the stress condition of the MIST, but not the Cyberball and RMSSD did not change significantly in either paradigm. These results show the distinct psychophysiological response that is evoked by each paradigm as the stress condition of the MIST elicited a significant physiological change and was experienced as more stressful, while this was not the case for the exclusion condition in the Cyberball. The EEG results from this study were surprising. Analyzed together, no significant change in any region could be identified, which contradicted our hypothesis of finding increased beta activity in the bilateral anterior insulae, seemingly the most consistent activity change across stress paradigms (Berretz et al., 2021). When both paradigms were analyzed separately, however, increased beta power in the left orbitofrontal cortex, left prefrontal region, and left as well as right temporal region was identified for the Cyberball paradigm. The MIST on the other hand resulted in increased alpha power in the left and right precuneus/PCC complex, thus replicating the main findings of chapter 4. These results confirm the highly specific neural response to each stress induction paradigm, but another explanation should also be considered. If the results of the Cyberball are taken together, it becomes difficult to assume that this paradigm is capable of consistently inducing a stress response. Although significantly increased negative affect was identified, participants did not rate the exclusion condition of the paradigm to be more stressful than the inclusion condition and no changes in physiological activity were identified. This implication is strengthened by previous literature, as no consistent cortisol increases were identified after

exposure to the Cyberball, even without the necessary adaptations for EEG research (Helpman et al., 2017; Vanhollebeke, Aers, et al., 2023; Zöller et al., 2010). The absence of significant effects when both paradigms are analyzed together might thus partly be caused by to the fact that no measurable stress response was elicited by the Cyberball, possibly caused by the different implementation compared to the original, non-ERP-compatible paradigm (Hartgerink et al., 2015; Vanhollebeke, Aers, et al., 2023).

This chapter provides an important insight into ESI, as it highlights its advantages while also indicating its limitations. The increased alpha activity in the precuneus/PCC complex, identified in the reactive phase in chapter 4, was replicated in this chapter and was found in the recovery phase during the MIST. This result strengthens the idea that SET leads to decreased precuneus/PCC activity in both the reactive and recovery phases of the stress response, and shows that this neural reaction seems specific to SET as it was not found in the Cyberball. This conclusion was also obtained in the article of Berretz and colleagues (2021) as precuneus/PCC deactivation was found in the meta-analysis where the Cyberball was excluded, while it was not present in the meta-analysis that included the Cyberball. This chapter shows the added value of ESI as its higher temporal resolution allows further research into the time-dependent changes of these cortical regions that cannot be captured by fMRI. On the other hand, however, increased beta activity in the anterior insulae was not found in either experimental study in this dissertation, while this result is the most consistent activity increase across stress induction paradigms (Berretz et al., 2021; Cacioppo et al., 2013; Kogler et al., 2015; van Oort et al., 2017; Wang et al., 2017). The most probable reason for this is the lower spatial resolution of ESI compared to fMRI, as the identified cluster is likely too small and is located too deep for consistent identification through means of EEG and ESI, especially in the absence of individual MRI scans.

Figure 1 provides an overview of the main findings of this dissertation as a function of both the stressor type and stress response phase. Taken together, the reactive phase of ostracism was investigated in chapter 3 where ERP results were systematically reviewed, and the recovery phase was investigated in chapter 5 where increased beta power in the left orbitofrontal and frontal region, and the left and right temporal regions was identified. Social-evaluative threat was investigated in all three phases. The anticipatory, reactive, and recovery phase were reviewed in chapter 2. The reactive phase was further investigated in chapter 4 and increased alpha power in the precuneus/PCC complex was found. Chapter 5 replicated this increased

alpha activity, and showed that SET results in decreased cortical activity of the precuneus/PCC complex both during and after stressor exposure.

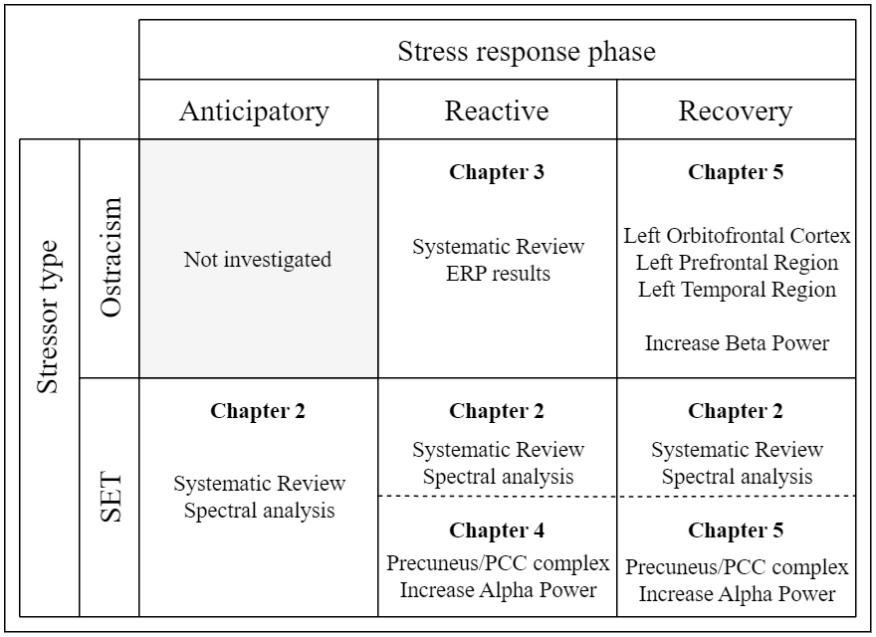

Figure 6: Schematic overview of the main findings of this dissertation as a function of stressor type and stress response phase.

Concluding this overview, it is worth returning to the two main objectives of the dissertation. Objective 1, **the critical evaluation of the psychosocial stress-EEG research field**, is reflected in chapter 2 and 3. Both chapters systematically review the respective research fields as chapter 2 evaluates spectral analyses during the various phases of the psychosocial stress response and chapter 3 evaluates ERP results during the Cyberball paradigm. Additionally, both chapters identify possible limitations in each field as chapter 2 identifies the ubiquity of frontal alpha and beta power, as well as FAA to investigate psychosocial stress while these measures might be insensitive to purely psychosocial stressors and further are influenced by volume conduction. Chapter 3 showed that the underlying neural mechanism of the P3b is not unique to ostracism, but rather a more general neural system activated by expectancy violations. Objective 2, **assessing the possible added value of ESI**, can be seen in chapter 4 and 5. In chapter 4, it was shown that source level EEG measures, derived through ESI, are sensitive to isolated psychosocial stressors in contrast to commonly employed sensor level measures. In chapter 5, it was shown that activity changes in several ROIs could be identified that align with previous fMRI literature. Chapter 5, however, also showed the limitations of ESI when no individual MRI scans are available as the small activity cluster in the bilateral insulae, the most consistent activity in fMRI research, could not be identified in either chapter 4 or 5.

2. Significant findings relative to other literature

Considering the results and conclusions summarized in the previous section, one might wonder how these results align with or contradict the broader research into the neural psychosocial stress response. In this section, the obtained results from the experimental studies are considered within this broader scope. First the sensor level results reviewed in chapter 2 and obtained in chapter 4 are considered within their respective field. Afterwards, the source level results are discussed. These will be given more attention as they are the main focus of the experimental studies presented in chapter 4 and 5.

2.1. Sensor level results

Our results regarding sensor level analyses are twofold: in chapter 2, spectral analysis EEG studies were reviewed, highlighting frontal alpha and beta power as well as frontal alpha asymmetry as the three most commonly employed measures (Vanhollebeke et al., 2022). Subsequent meta-analyses of these measures showed that frontal alpha power decreases regardless of the stress response phase, while both beta power and FAA were not consistently affected by psychosocial stress across stress phases. In chapter 4 frontal theta, alpha, and beta power were shown to be insensitive to a purely psychosocial stressor without the presence of commonly co-occurring stressors such as time pressure or increased difficulty of cognitive tasks (Vanhollebeke, Kappen, et al., 2023). This result replicated an earlier study of Ehrhardt and colleagues (2021), but it is important to keep in mind that both studies employed subtle psychosocial stressors, so the possibility remains that stronger psychosocial stress paradigms do elicit robust changes in these measures.

Before discussing this body of literature and comparing it with the results of this dissertation, an important development in this field should be acknowledged and addressed: the majority of recent articles employ machine learning (ML) or deep learning (DL) for the detection of psychosocial stress, which is often referred to as "mental stress" (Giannakakis et al., 2019; Katmah et al., 2021). The reasons for this development are obvious: artificial intelligence (AI) has the capability to find complex patterns in data that are difficult or even impossible to spot by commonly employed statistical methods or human insight. Considering the complexity of neuroimaging data, AI provides an excellent avenue for uncovering novel neural mechanisms or "brain states" (e.g., not stressed or stressed) in a data-driven way that are difficult to identify through a theory-driven approach. Additionally, the increased capabilities of data collection and increased availability of datasets containing thousands of individuals

(Littlejohns et al., 2020; Markiewicz et al., 2021; Zbontar et al., 2018), combined with the increased computation capabilities at a low cost and available open source ML toolboxes (Leenings et al., 2021; Pedregosa et al., 2011) has made AI available for many researchers across the world. In the field of neuroscience, AI is consequently used to address some of the most difficult and pressing problems such as the identification of biomarkers for neurological and psychiatric disorders and the development of individualized disease trajectories and treatment plans (Bzdok & Yeo, 2017; Lee et al., 2018; Ramos-Lima et al., 2020; Tanveer et al., 2020). Regarding EEG, the increased availability of low-cost, wearable EEG systems has lead to an increased interest in the development of mental stress prediction models as it might aid the identification of individuals at risk of developing burnout or depression (Sawangjai et al., 2019).

ML focused articles have a fundamentally different approach to research when compared to articles that employ classical statistical analysis (i.e., chapter 4 and 5). While *inference* is the goal of statistics, articles employing ML are more concerned with *prediction* (Ij, 2018). Returning to the psychosocial stress-EEG field, this translates into articles that aim at predicting whether certain combinations of EEG features (i.e., independent variables) reflect a "stress state" or a "non-stressed state" through binary or multiclass classification (Katmah et al., 2021). This focus shift results in more attention given to the construction and validation of the employed ML models while features from the EEG signals such as spectral power, FC, or graph measures are generated in excess and not analyzed directly before the most performant are selected through feature selection procedures. Comparing our results with these articles is thus best conducted by comparing what features are commonly chosen through feature selection.

The review of Katmah and colleagues (2021) provides an excellent overview for this comparison. Regarding spectral power features, the best performing frequency band is the alpha band (with average accuracy above 90% for the binary classification problem of "no stress" versus "stress"), followed by the beta band (with average accuracy around 80%) (Katmah et al., 2021). Comparing this with our own results presents an interesting intitial conclusion. Both features that result in the best performing classifiers are two features that were shown to be insensitive to psychosocial stressors (Ehrhardt et al., 2021; Vanhollebeke, Kappen, et al., 2023). It would, however, be incorrect to dismiss these studies. "Mental stress", the rubric of stressors investigated by these studies, can contain cognitive stressors as well so the cognitive tasks or time limits that often co-occur in the employed paradigms might be considered problematic

within the framework of this dissertation, but are not detrimental when considered outside its scope (Giannakakis et al., 2019; Katmah et al., 2021). It could even be argued that the co-occurrence of multiple stressor types is a better reflection of real-life events as these often present multiple stressors simultaneously . Additionally, many studies do not solely rely on only alpha or beta power at frontal electrodes, but employ a vast array of EEG measures that likely better capture stress-related changes.

These studies, however, have several limitations and issues that should be considered for future research. First and foremost is the fact that, due to the focus on prediction rather than inference, these studies provide less information of what exactly changes due to the presence of either psychosocial or mental stressors. Due to the general "black box" approach that many ML models exhibit, even if high performance is obtained it remains difficult to understand what exactly was identified by the models. This critique should only be interpreted within this dissertation and should not be taken as a fact, but it is worth reflecting on the question as to what exactly these studies contribute to our understanding of the underlying neural mechanisms of the stress response.

Secondly, the data-driven approach that is taken in these studies has assumptions that are often not validated. Most important are the implicit assumption that the EEG data captured during the non-stressed and stressed states can clearly be seperated, that the ML model has truly learned the difference between stress states rather than spurious changes, and that the dataset is large enough to obtain a prediction model that can consistently identify stress rather than overfit on the dataset itself. Extending this discussion to other classification problems that have been studied in the field of neuroscience, research has shown that these assumptions are often difficult to satisfy. The assumption that mental states are clearly defined and separatable has been critisized for a long time, with the Research Domain Criteria (RdoC; Cuthbert & Insel, 2013) framework as a proposed alternative to the Diagnostic and Statistical Manual of Mental Disorders (DSM; APA, 2013) likely being the best known example. Spurious results are also a significant problem, as individual studies report high performance on their initial dataset while this performance cannot be replicated on similar datasets. A recent example of this is the study by Winter and colleagues (2024), who exhaustively evaluated various MRI modalities for the classification of patients with MDD and healthy controls. Their results were sobering, showing that neither individual modalities nor multimodal analyses were capable of consistently separating both classes (Winter et al., 2024). Multiple systematic reviews however can be found that show multiple studies achieving high accuracy for this classification problem (Gao et al.,

2018; Lee et al., 2018). Considering that depression is a serious psychiatric disorder while the studies reviewed by Katmah and colleagues (2021) often employ subtle stressor paradigms, it should be kept in mind that these studies might not be able to replicate their initial findings when novel datasets are analyzed. Necessary sample size has also been a point of significant discussion. Recently, an article by Marek and colleagues (2022) posited that neuroimaging datasets require thousands of individuals to establish reliable, reproducible biomarkers. Several rebuttals have been published since its release that argue that ML models can be trained on smaller datasets for reliable prediction, yet hundreds of individuals are required (DeYoung et al., 2022; Rosenberg & Finn, 2022). Returning to the studies reviewed by Katmah and colleagues (2021), all but one study had less than 100 subjects in their datasets. Of high importance here is that these limitations are not unique to machine learning nor to the studies reviewed by Katmah and colleagues (2021), as limited datasets and implicit divisions of "non-stressed" and "stressed" states are also present in chapter 4 and 5.

Taken together, our sensor level results hint at a significant problem in the broader psychosocial stress research field as the most commonly employed measures are frontal alpha and beta power, while our (and other) results showed that these measures are not sensitive to purely psychosocial stressors (Ehrhardt et al., 2021; Vanhollebeke, Kappen, et al., 2023). This problem, however, should only be considered within the scope of this dissertation, as most of these studies investigate mental, not psychosocial, stress. The co-occurrence of additional stressors is therefore not necessarily an issue in the broader scope of stress research. Almost all sensor level EEG studies that investigate psychosocial stress, however, employ AI for the detection of mental stress. Therefore less information can be extracted from these studies for future research. Additionally, several challenges related to ML further hinder the potential of this research avenue.

2.2. Source level results

The source level results of chapter 4 and 5 can be divided into two parts: the increased alpha power in the precuneus/PCC complex identified in both the reactive and recovery phase and increased FC between the left and right precuneus in the alpha band during the reactive phase due to SET (chapter 4 and 5), and the increased beta activity in the left orbitofrontal and frontalregion, and left and right temporal regions during recovery from ostracism (chapter 5).

As stated before, increased alpha power likely reflects decreased activity of the precuneus/PCC complex (Allen et al., 2004; Jensen & Mazaheri, 2010; Mathewson et al., 2011). This result best aligns with the fMRI meta-analysis of Berretz and colleagues (2021), where decreased precuneus/PCC activity was identified when the Cyberball was not included in the meta-analysis. This inverse link between precuneus/PCC activity and stress has also been identified in some studies. A recent article directly investigating this link showed that decreased precuneus/PCC activity was linked with increased levels of both self-reported stress and skin conductance responses during emotion regulation (Guendelman et al., 2022). Similarly, Pires and colleagues (2018) found that decreased self-reported stress was linked with increased precuneus/PCC activity, again hinting at this inverse relationship. When other individual fMRI studies are considered that found changes in precuneus/PCC activity during psychosocial stress, results are however less uniform (van Oort et al., 2017). Several studies identify increased precuneus/PCC activity in the reactive phase (Dedovic et al., 2014; Lederbogen et al., 2011; Lord et al., 2012), but others found decreased activity (Akdeniz et al., 2014; Albert et al., 2015) while all studies employed the MIST or variants of it. fMRI-FC studies regarding the precuneus/PCC are also not consistent as either decreased FC between the precuneus/PCC and the amygdala (directly after stress exposure; Maron-Katz et al., 2016) or increased amygdala-precuneus/PCC FC one hour after stress induction (Veer et al., 2011) has been reported, although the time difference might explain this opposition (see chapter 1, section 2.2.3.4.2.).

Considering studies that employ social feedback without manipulation, which might not be stressful in itself although SET is potentially present, the complex reactions of the precuneus/PCC activity are again encountered. Investigating the influence of acceptance or rejection from either low- or high-interest peers, Guyer and colleagues (2012) showed that the precuneus/PCC was more deactivated during rejection from low-interest peers than during acceptance of either low- or high-interest peers. Positive social feedback on the other hand has been linked with increased activity of the complex (Sherman et al., 2018). One personality trait,

self-esteem, has also been heavily implicated in precuneus/PCC activity differences with regard to social feedback as high self-esteem was linked with increased precuneus/PCC activity during negative feedback while low self-esteem was linked with decreased activity (Van Schie et al., 2018; Yang et al., 2016). These studies again hint at an inverse relationship between the valence of the feedback and the activity of the precuneus/PCC.

Precuneus/PCC activity alterations has also been identified in several stress-related mental disorders. In individuals with PTSD, precuneus/PCC activity is mostly reduced during the presentation of a variety of stimuli. An elegant possible explanation for this is given by Andrewes and Jenkins (2019), who propose that the deactivation reflects *"a focus on threat at the expense of self-reflection"* (Andrewes & Jenkins, 2019). Similarly, patients with SAD also exhibit decreased precuneus/PCC activity compared to healthy controls (Gentili et al., 2009; Warwick et al., 2008). Finally, patients with MDD often show decreased precuneus/PCC activity at rest (Sheline et al., 2010; Zhu et al., 2012), but considering FC with several other regions identified in psychosocial stress response, more varied results are found (Castanheira et al., 2019; Dai et al., 2019; Kerestes et al., 2014). Of note here is that these studies do not investigate disorders with a focus on psychosocial stress, so deactivation of the precuneus/PCC should not be considered as direct evidence or support for our own findings.

All the studies discussed above have used fMRI, so one might wonder whether there are EEG studies that align or contradict our findings. These studies, however, are few in number and often do not directly investigate psychosocial stress. No studies that employed spectral analyses and ESI for the investigation of psychosocial stress could be identified. A few ERP studies, however, employed ESI for the identification of neural generators of ERP components during social feedback tasks. One study identified the precuneus as a likely generator of an early negativity component in a shameful context (Sánchez-García et al., 2021). Another study explored the effects of expectancy violations (which was found to be the best explanation of the P3b in chapter 3) within a context of social rewards. Here the precuneus/PCC was again identified as the generator of a late positive wave (P400-700) during incongruent trials (Du et al., 2014). These results, however, are difficult to compare with our own results of decreased precuneus/PCC activity as it has been proposed that *evoked* neural activity, identified through ERP analysis, might be different from *induced* activity assessed by spectral analyses (David et al., 2006). The only conclusion that can be obtained from these studies is thus that the precuneus/PCC are involved in social feedback, but neither confirmation nor conflict with our own results can be inferred.

Several EEG studies, however, can be identified that employ ESI for the investigation of differences between healthy controls (HCs) and patients with stress-related mental disorders. It was shown that patients with PTSD showed increased activity in the precuneus/PCC compared to HCs, but this activity was located in the theta, not alpha band (Imperatori et al., 2014). Increased FC in the alpha band was additionally found between the precuneus/PCC and the parietal lobe, resulting in the conclusion by the authors that the precuneus/PCC is a region of high importance regarding PTSD (Imperatori et al., 2014). Al-ezzi and colleagues (2021) investigated patients with SAD with a focus on FC abberation in the DMN. They found that these patients exhibited increased FC (measured by partial directed coherence) between the precuneus/PCC and mPFC and lateral parietal cortex in both the delta and alpha band. They further found that of these regions, the precuneus/PCC had the the most causal influence on the other regions in both frequency bands. A study investigating patients with MDD, however, found lower instead of higher PCC alpha power in the patients with MDD compared to HCs (Pizzagalli et al., 2002). Similarly to the fMRI studies investigating these disorders, no focus was given to psychosocial stress so these studies do not provide direct evidence for our own results, but reconfirm the importance of the precuneus/PCC in stress-related disorders.

Taken together, the result of decreased cortical activity in the precuneus/PCC identified in chapter 4 and 5 largely aligns with the broader scope of psychosocial stress and negative social feedback, but given the significant variability of results and differences regarding neuroimaging method and analysis type this conclusion should be considered with some caution.

The precuneus/PCC complex is an important region of the DMN, and several studies have linked activity in these regions with internally focused, self-reflective thoughts (Buckner & Carroll, 2007; Fransson & Marrelec, 2008; Johnson et al., 2002; Lou et al., 2004). Decreased activity of this complex has subsequently been observed when participants performed tasks that were more externally-focused (Lou et al., 2004). This trend has been incorporated in a model of PCC function by Cavanna and Trimble (2006), who posit that increased internal focus is reflected by increased PCC activity. Our results thus might indicate that due to the presence of a psychosocial stressor, the focus is more external for the regulation and adaptation of external threats (Cabanis et al., 2013; Cavanna & Trimble, 2006; Leech & Sharp, 2014).

This conclusion, however, should be considered with caution for several reasons. First and foremost is the danger of reverse inference (Poldrack, 2006). The fact that our results align with the model of Cavanna and Trimble (2006) is no direct proof that this interpretation is the correct one, as precuneus/PCC activity changes have been identified in a range of cognitive processes (Cavanna & Trimble, 2006). Additionally, the fact that increased alpha power is found in both the reactive phase and the recovery phase does not necessarily mean that it represents the same cognitive process or effect as it is possible that different underlying processes resulted in the same measureable change in the EEG signal. Considering that chapter 5 investigated the recovery phase, it is possible that emotion regulation strategies were employed by the participants, as some regulation strategies have been linked with decreased precuneus/PCC activity as well (Messina et al., 2021; Seo et al., 2014). Aside from either more external focus or emotion regulation, it has also been proposed that PCC/precuneus activity during the recovery phase might reflect memory consolidation of salient emotional stimuli given its increased connection with the amygdala during stress recovery and its role in autobiographical memory processing (Cavanna & Trimble, 2006; Vann et al., 2009). Finally, the implicit assumption that only one underlying cause is the sole reason for the observed change is also not necessarily true. Considering the large size of the precuneus/PCC complex (see figure 2), the limited spatial resolution of the obtained ESI solution, and the averaging process that occurs to obtain the final time series, it is possible that multiple neural processes are captured, further complicating any inference as to what these results reflect.

Some final reflections should be made with regard to this result. Firstly, throughout chapter 4 and 5, as well as this discussion, the term "precuneus/PCC complex" is employed. The statistical results, however, were performed for the left and right precuneus and PCC (chapter 4) or left and right precuneus/PCC (chapter 5) separately. The reader might thus wonder why no attention is given to any possible laterality or precuneus/PCC differences regarding these results. This was done for two reasons. In the psychosocial stress fMRI literature, these regions are often deactivated together rather than identifying clear separate neural patterns, hinting at the fact that no clear functional separation can or should be made with regard to this complex. Additionally, the limited spatial resolution and subsequent spreading of the ESI results further make it difficult to be certain that completely different neural activity is observed in these regions. This possible overlap is more likely since, contrary to the computation of AEC (chapter 1, section 2.2.4.6.3.), no removal of a possible zero-lag common signal is conducted for the relative power computation (chapter 1, section 2.2.4.6.2.).

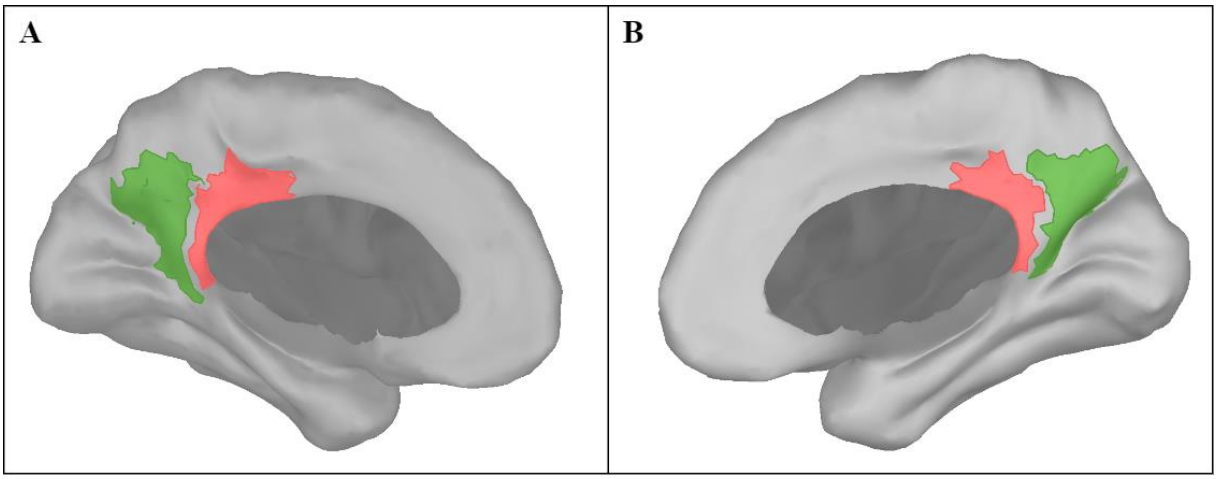

Figure 7: Visualization of the considered regions of the USCBrain atlas that together form the precuneus/PCC complex on a smoothed cortical surface. **A)** Left precuneus inferior (green) and PCC (red). **B)** Right precuneus inferior (green) and PCC (red).

Secondly, although a significant increased functional connection between the left and right precuneus in the alpha band was identified in chapter 4, it was given little attention. This was done because it was not replicated in chapter 5, while the power changes were, and because no other significant FC changes were identified in either study. It is important to consider the study of Palva and colleagues (2018) here, as they showed that spurious connections might still be present after the removal of the zero-lag common signal during the computation of the amplitude envelopes (Palva et al., 2018). The left and right precuneus are located near each other, and the study that identified this connection employed fewer electrodes, and thus had lower spatial resolution (Allouch et al., 2023) than the study that did not find this change. It is therefore possible that this connection was spurious.

A final reflection should be made on the direction of this result. In both studies, a significant *increase* in alpha power was found. In chapter 2, however, it was shown that alpha power *decreased* throughout the different stress phases, and our meta-analysis indicated that this effect is the most consistent of all employed EEG measures (Vanhollebeke et al., 2022). This contradiction, however, has several possible explanations. First is the fact that sensor level alpha power was almost always considered at frontal electrodes in chapter 2, while the precuneus and PCC are located in the parietal lobe. Secondly, in chapter 4 it was shown that frontal alpha power does not change significantly due to psychosocial stressors alone, a result strengthened by the study of Ehrhardt and colleagues (2021). Finally, the validity of sensor level spectral analyses has been questioned by Schaworonkow and colleagues (2022), as the neural activity measured by frontal electrodes also contains a large amount of activity from occipital sources (Schaworonkow & Nikulin, 2022).

Taken together, our first result shows that social-evaluative threat, regardless of the employed paradigm, results in increased alpha power of the precuneus/PCC complex and that this effect is present both during the reactive and recovery phase. This decreased cortical activity might represent a temporary external focus for the adaptation and regulation of external threats, although other processes such as emotion regulation or autobiographical memory processing possibly also explain this effect. Therefore future research should further elucidate its precise origin.

The other results are the increased beta power in the left orbitofrontal and frontal region, and left and right temporal regions during the recovery phase of the Cyberball, identified in chapter 5. Contrary to alpha power, beta power is believed to reflect cortical processing (Chikhi et al., 2022; Engel & Fries, 2010; Miller, 2007; von Stein & Sarnthein, 2000). These results thus likely indicate that the left orbitofrontal, frontal, and bilateral temporal regions are more active directly after the exclusion condition of the Cyberball. Each region will be discussed separately.

Increased activity in the left orbitofrontal region is consistently found when participants are exposed to the Cyberball paradigm as several systematic reviews and meta-analyses have identified this region in their analysis (Cacioppo et al., 2013; Mwilambwe-Tshilobo & Spreng, 2021; Vijayakumar et al., 2017). Our result therefore aligns with the broader fMRI literature under the assumption that beta power reflects cortical activity and excitability. This increase in activity possibliy reflects social-cognitive processes, as increased orbitofrontal cortex activity has been identified in studies that employ self-reflective social and evaluative processes (Burnett et al., 2011; Pfeifer et al., 2011). Another line of evidence also supports this notion, as lesions in the orbitofrontal cortex have been linked with dysfunctional social-cognitive and emotional processes (Bechara et al., 2000). This result thus implies that ostracism results in increased engagement of social-cognitive processes. No EEG studies could be identified that investigated this region with regards to ostracism.

Activity increases in the left frontal region are also commonly identified during ostracism (DeWall et al., 2012; Masten et al., 2011; Maurage et al., 2012; Radke et al., 2018), although deactivation of this region has also been reported (Bolling et al., 2011; Gradin et al., 2012; Kawamoto et al., 2012). The left frontal region has been heavily implicated in cognitive control and emotion regulation (Crowell et al., 2013; Ochsner & Gross, 2005; Torre & Lieberman, 2018). It has also been proposed that this region regulates amygdala functioning and thus controls and inhibits the affective response originating from the amygdala, again

highlighting its potential role in emotion regulatory processes (Torrisi et al., 2013). Considering the high variability, however, it remains unclear how exactly ostracism influences this cortical region and how exactly our results should be interpreted. Therefore future research should further investigate this region with regards to ostracism. Again no EEG studies were found that reported effects related to this region in the context of ostracism or psychosocial stress.

Finally, increased activity of the left and right temporal regions has also been identified in Cyberball studies (Wang et al., 2017). Similarly to the two previously discussed regions, it is also believed that this region is employed for emotion regulatory processes (Blair et al., 2007; Ochsner et al., 2004).

Taken together, these results imply that all identified regions are involved in emotion regulatory, social-cognitive processes. Considering that the analyzed EEG data reflects the recovery phase, this explanation seems logical as the Cyberball did result in significantly increased negative affect and emotion regulation by the participants is to be expected. Several considerations need to be made here however.

Firstly, the selection of USCBrain scouts that represent the brain regions of interest should be considered. As can be seen in Figure 3, multiple ROIs were taken together for the investigation of each region, resulting in large regions of the cortex that are considered. This was done for two reasons: the limited spatial resolution and spread of the ESI solution and the variability of fMRI results across fMRI studies, systematic reviews, and meta-analyses (Berretz et al., 2021; Cacioppo et al., 2013; Dedovic et al., 2009; Kogler et al., 2015; Mwilambwe-Tshilobo & Spreng, 2021; van Oort et al., 2017; Vijayakumar et al., 2017; Wang et al., 2017). The size of these regions, however, makes it impossible to infer from where exactly the measured activity comes from (i.e., which specific ROI) and thus limits the comparison of our results with fMRI studies. This is of high importance for the frontal regions as various subregions have distinct functions, so the proposed explanations should be considered with caution, but is especially important when the orbitofrontal region is considered, as this region is located near another important region: the medial prefrontal cortex (Beer et al., 2010). Given its deep location within the brain and the large size of the considered ROI, it is possible that the activity of these regions is not consistently separated, and our results might therefore (partly) reflect mPFC activity. As discussed in chapter 1, section 2.2.3.4.2., mPFC-amygdala connectivity has been investigated directly after stress exposure (i.e., the time window considered in chapter 5), and was found to be increased (Banks et al., 2007). This increased connectivity is believed to reflect the heightened control of the PFC on the amygdala.

Considering this, it might be possible that the increased beta power of the orbitofrontal cortex might actually indirectly reflect this effect.

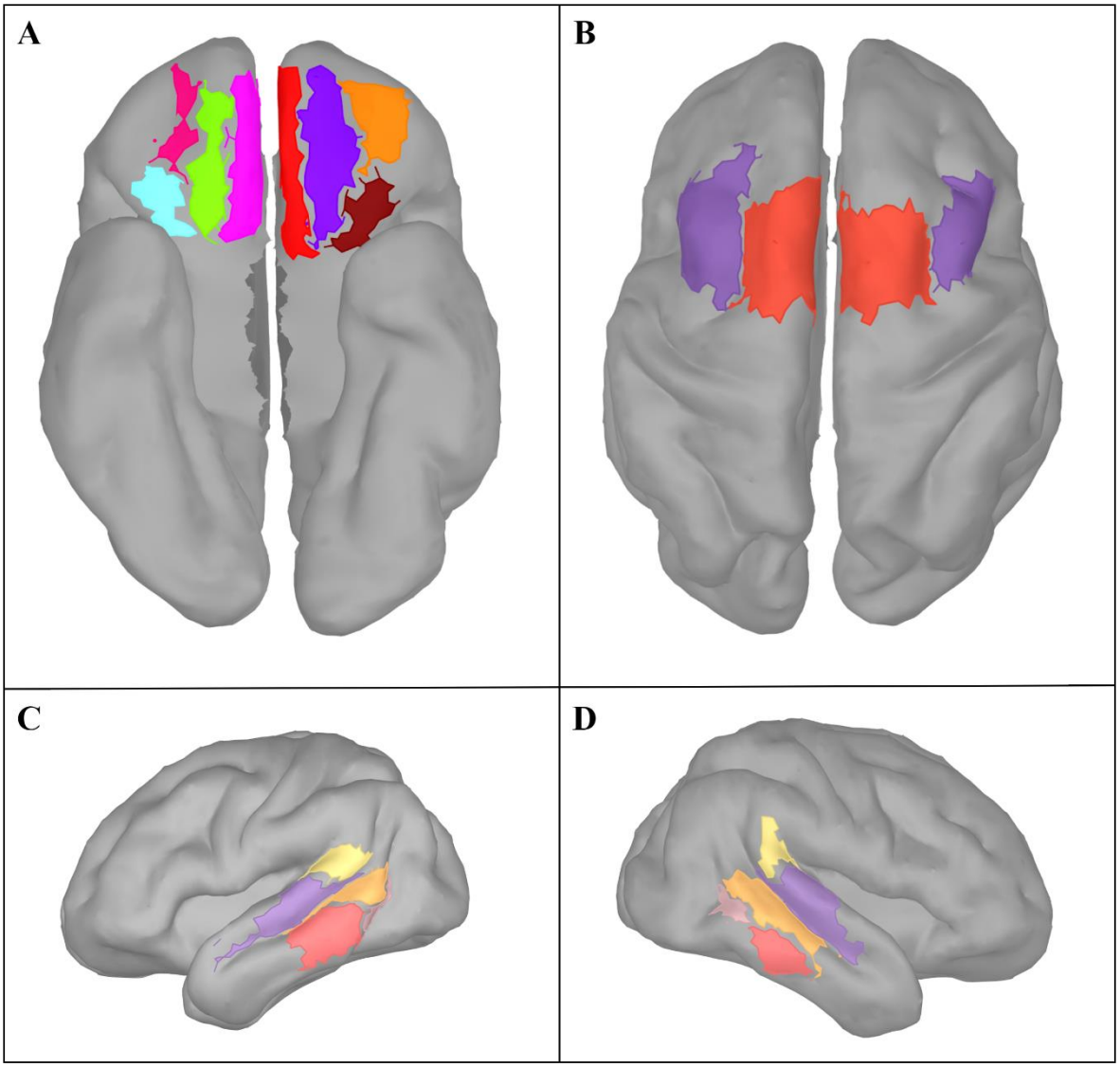

Figure 8: Visualization of the USCBrain regions (Joshi et al., 2022) that were combined to obtain a single time series of the brain region of interest on a smoothed surface. **A)** Regions that are considered for the orbitofrontal region, viewed from below. **B)** Regions that are considered for the frontal region, viewed from above. **C)** Regions that are considered for the left temporal region. **D)** Regions that are considered for the right temporal region.

Secondly, three of the four regions that exhibit significant beta power changes are located in the left hemisphere. This implies that ostracism results in laterized neural changes, which does not correspond with the fMRI literature, aside from the orbitofrontal cortex (Burnett et al., 2011; Pfeifer et al., 2011). It is possible that the combination of multiple ROIs might have resulted in the blurring of multiple neural sources, therefore "hiding" the activity of interest in unrelated activity. This conclusion should therefore be considered with severe caution and future research should evaluate whether the left laterization is indeed present during the recovery of ostracism.

Taken together, the left orbitofrontal, frontal, and bilateral temporal regions exhibited increased beta power during the recovery phase of ostracism. All four regions have been implicated in emotion regulatory processes, implying that participants engaged in emotion regulation following ostracism. Given that the regions are large, however, this conclusion should be considered with caution as it is possible that neural activity from nearby sources are (partly) present in the analyzed time series.

3. Limitations

The reader will by now surely have noticed that the author approaches the psychosocial stress research field with a critical mindset. Both systematic reviews address assumptions present in the respective research fields that might be incorrect or hinder further progression (i.e., the influence of volume conduction on sensor level measures in chapter 2; the assumption of an ostracism-specific neural alarm system in chapter 3). Additionally, both experimental studies address possible limitations that are present. In chapter 4, it was shown that commonly employed sensor level EEG measures are insensitive to psychosocial stressors alone (Vanhollebeke, Kappen, et al., 2023). Chapter 5 further highlighted that the evoked neural psychosocial stress response is highly dependent on the specific stressor paradigm that is employed. Considering this critical approach to the research field, it is only fair that an equally critical reflection is made upon the scientific work that is presented in the current dissertation.

3.1. Systematic reviews

The main limitation of the systematic reviews are the strict inclusion- and exclusion criteria. This limitation is present in all systematic reviews, as a balance needs to be found between identifying the relevant literature and keeping the review focused on the research question at hand, yet should be considered as additional studies might have led to more informed conclusions. This is most prominent in chapter 3, as this limitation resulted in the absence of ERP studies that present results from specific patient populations. The presence of studies that included patients with borderline personality disorder and social anxiety disorder, however, proved to be crucial for the final conclusion that the P3b was an index of expectancy violations (Weinbrecht et al., 2018, 2021), and it is thus possible that clearer conclusions could have been obtained for other ERP components aside from the P3b if additional studies would have been included.

3.1.1. Experimental design

Four limitations can be identified regarding the experimental design of chapter 4 and 5: the absence of counterbalancing, the different times throughout the day that participants completed the paradigm, the high homogeneity of the participant samples, and the absence of information regarding life events.

The most important limitation is the absence of counterbalancing, as the control condition was always presented before the stress condition. This approach was employed as the initiated stress response would likely infer with the control condition if it was presented afterwards, considering that the cortisol response has a peak 30 minutes after stress induction (Goodman et al., 2017), and alterations in neural activity have been identified for up to two hours after stress induction (Vaisvaser et al., 2013). The absence of counterbalanced conditions, however, makes it impossible to be certain that the identified changes in the studies are solely related to the presence or absence of the psychosocial stressors as additional factors such as tiredness or habituation could also have influenced these results (Brooks, 2012). This limitation is most prominent in chapter 4 as arousal was found to be decreased, rather than increased and its results should therefore be considered with caution (Vanhollebeke, Kappen, et al., 2023). Of note here is that the replication of the increased alpha activity in the precuneus/PCC complex in chapter 5 as well as its accordance with the fMRI literature (Berretz et al., 2021) does significantly diminish the chance that other factors are the cause for this result. The fact that it was only found in the MIST paradigm signifies its specificity to SET, which is also in line with the fMRI literature, and further strengthens this result (Berretz et al., 2021).

The second limitation is the different times throughout the day that participants completed the experimental paradigms as data was collected between 9 AM and 6 PM in blocks of three hours. This can be considered a limitation because stress reactivity is not static, but varies throughout the day as it is influenced by the circadian rhythm (Koch et al., 2017). This makes it possible that the stress response differs between participants as a function of time. This limitation was partly avoided by the within-subjects designs that were employed, as both the control and stress condition were consequently obtained in close succession. Additionally, participants needed to complete both paradigms in the same time window on both days in chapter 5 to control for this possible confounding effect. Nevertheless, it still remains possible that this variation might have had an influence on the results.

The third limitation regarding the experimental design is the high homogeneity of the examined population samples. The participant samples are mostly composed of young, Dutch speaking University students and therefore the obtained results and conclusions are limited in their external validity. Research has shown that differences in age and gender have a significant influence on the stress response, so the results from this dissertation do not necessarily apply to other sections of the wider population (Kudielka, Buske-Kirschbaum, et al., 2004). In recent years, is has further been shown that individuals from Western, Educated, Industrialized, Rich,

and Democratic (WEIRD) countries are not a good representation of the "average" individual across the world and in reality are actually outliers in many behavioral and emotional processes, further limiting the generalizability of our results (Henrich et al., 2010).

The final limitation is the fact that no information regarding prior stressful experiences or life events was collected in the experimental studies. Research has shown that significant stressful events in life have a substantial influence on the stress response and stress reactivity later in the lifespan of the individual (Compas, 1987; DeLongis et al., 1982). Life events are especially important when they are encountered in childhood or adolescence, and individuals that sadly experienced severe aversive events early on are more likely to develop mental health complications later in life (McLaughlin et al., 2014, 2019). Distinct alterations in the stress systems related to childhood averse events have also been noted on a neurobiological level. Early life adversity has been shown to significantly damage the development of the amygdala, hippocampus, and prefrontal cortex (Tottenham & Sheridan, 2010; VanTieghem & Tottenham, 2018), and this damage seems to result in dysfunctional control of the stress systems, leading to increased HPA axis, inflammatory, and immune reactions to stressors (Danese & McEwen, 2012). The absence of this information when investigating the acute psychosocial stress response might therefore have influenced the results.

3.1.2. EEG analysis

Regarding the EEG analysis, several limitations can be identified. The first limitation is manual interference. In chapter 4 some preprocessing steps were conducted manually (i.e., the identification of "bad" channels and the selection of ICA components that contained artifactual components). Although manual selection based on visual inspection is commonly employed in EEG research, it is possible that this approach introduces biases in the subsequent analyses as the exclusion of channels or ICA components can vary between researchers. Another potential issue with manual interference is that the analysis is not completely reproducible by external parties. This is especially important as several scientific fields, including neuroscience, have low replication rates (i.e., results from an initial study cannot be replicated by external parties in another study; Button et al., 2013; Maxwell et al., 2015; Miłkowski et al., 2018). Although the results are not yet public, the project called "EEGmanylabs" is currently attempting to replicate 20 highly influential EEG studies (Pavlov et al., 2021). One concern raised in this article is the so-called "experimenter degrees of freedom" whereby manual adjustments to preprocessing pipelines can have a significant influence on the final analysis results, thus highlighting this limitation (Pavlov et al., 2021).

Two possible limitations can be identified in the ESI procedure: the usage of finite element modeling (FEM) for the head model creation and the restriction of dipole orientation. Although FEM provides more realistic headmodels as BEM and thus *theoretically* is the better approach for ESI (Clerc et al., 2002), in both experimental studies a template MRI scan was employed as no individual scans were available. Therefore the employed headmodel does not necessarily aid the ESI solutions because it is possible that, given to the increased detail of the headmodel due to the FEM approach, morphological differences between the participants and the template headmodel are in reality more accentuated. The restricted orientation of the dipoles to be normal to the cortical surface, rather than employing an unrestricted orientation, suffers from the same problem. Differences in cortical folding between participants and the template might influence the source distributions that are obtained in both studies. It should be mentioned, however, that the aggregation of dipoles (with orientation flipping) to obtain a single time series for each ROI of the USCBrain atlas does negate these limitations significantly.

Aside from technical limitations regarding the EEG analysis, two conceptual limitations should be considered: the selection of brain regions and frequency bands for investigation. As stated in both chapter 4 and 5, selection of brain regions was based on previous fMRI literature given the many available systematic reviews and meta-analyses (Berretz et al., 2021; Cacioppo et al., 2013; Dedovic et al., 2009; Kogler et al., 2015; van Oort et al., 2017; Wang et al., 2017). This approach is theory-driven, and is a valid approach to research, but it limits the scope of the investigation. An argument could be made that a more data-driven approach for the selection of ROIs would have resulted in a better representation of which regions best represent the results of the fMRI literature. This approach, however, would likely result in the inflation of effect sizes as the most optimal combination of regions is easily identified by simply testing all possible combinations and selecting the combination of ROIs resulting in the largest difference across conditions. Considering that the studies in chapter 4 and 5 are the first that employ ESI regarding psychosocial stress, however, a completely data-driven approach would perhaps have been more appropriate as the imperfect mapping of fMRI results to ROIs of the employed atlas might have hindered further insights.

The process of mapping fMRI results to USCBrain ROIs deserves a more in-depth consideration as it is a vital step in both experimental studies. Of special interest here is the mapping of the anterior insulae (combined with parts of the inferior frontal gyrus; Berretz et al., 2021) to USCBrain ROIs as this result is the most consistent in fMRI research (Berretz et al., 2021; Cacioppo et al., 2013), but was not replicated in either experimental study. It should be noted that the following discussion can be applied to the other ROIs investigated throughout this dissertation.

The identified region by Berretz and colleagues (2021) is visualized in Figure 2A, and the USCBrain regions of interest (ROIs) that lie closest to the anterior insula are shown in Figure 2B. The fundamental question here is: *"Which ROI or combination of ROIs is most likely to represent the fMRI result adequately?"*. This question is nontrivial given the large amount of factors that will influence the final result. Considering the inherent limited resolution of ESI and the (relatively) deep location of the anterior insula within the brain, only selecting the anterior insula ROI is an optimistic (and even naive) approach as the neural activity across different participants would almost certainly not be captured adequately. The opposite approach would be to select all ROIs that are located close to the anterior insula, but this approach would likely result in the inclusion of activity from other prefrontal regions. Knowing that the prefrontal cortex has a significant role in the psychosocial stress response, and many subregions each conduct specific functions throughout the response, this approach thus has the risk of including confounding neural activity (Arnsten, 2009; McEwen et al., 2016).

The results of Berretz and colleagues (2021) should, however, also be considered critically as it is the result of a meta-analysis employing Activation Likelihood Estimation (ALE ; Laird et al., 2005; Turkeltaub et al., 2002). In brief: ALE uses peak coordinates from the individual studies of interest and models them as 3D gaussian probability distributions. These distributions are subsequently considered together and clusters are defined as either significant or not based on several criteria such as number of foci, size of the cluster, and multiple comparison correction method (Laird et al., 2005). ALE has been rigorously tested an validated, so the results of Berretz and colleagues (2021) are without a doubt valid, but they should be interpreted as an activation cluster obtained through a multitude of complex statistical processes, where small differences in tresholding criteria can yield alterations in cluster size and location (Laird et al., 2005).

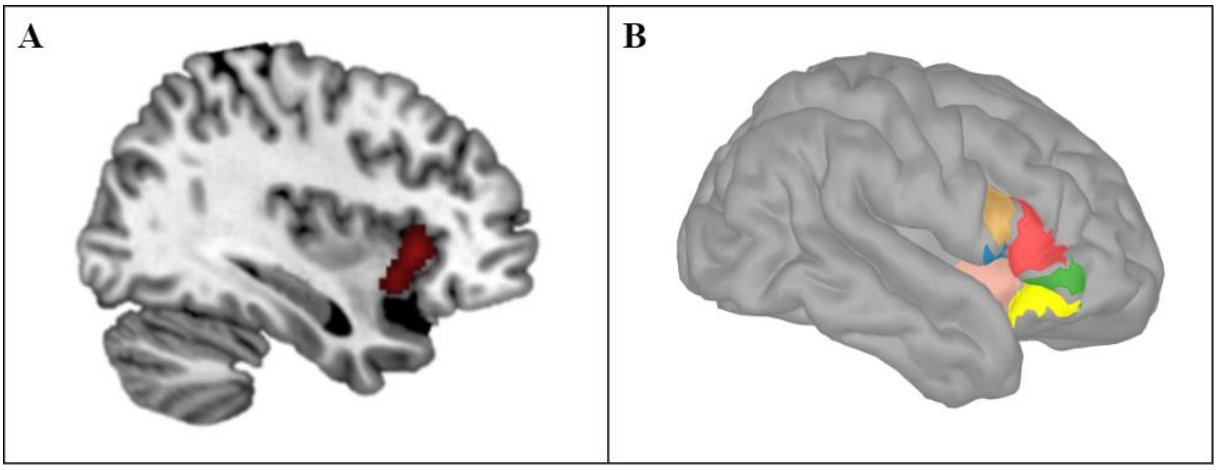

Figure 9: Representation of the difficulties regarding the mapping of fMRI results to USCBrain ROIs. **A)** Figure from the article of Berretz and colleagues (2021) showing the results of the meta-analysis including all experimental paradigms. **B)** Visualization of the ROIs of the USCBrain atlas that lie closest to the identified result from Berretz and colleagues (2021). Anterior Insula is shown in salmon pink, Pars Opercularis – inferior is shown in blue, Pars Opercularis – superior is shown in gold, Pars Triangularis – posterior is shown in red, Pars Triangularis – middle is shown in orange, Pars Triangularis – anterior is shown in green. **Copyright:** figure A is reprinted from Neuroscience & Biobehavioral Reviews, 124, Gesa Berretz, Julian Packheiser, Robert Kumsta, Oliver T. Wolf, Sebastian Ocklenburg, The brain under stress—A systematic review and activation likelihood estimation meta-analysis of changes in BOLD signal associated with acute stress exposure, 89-99., 2021, with permission from Elsevier. **Note:** both the copyright agreement and written permission from the corresponding author can be found in the supplemental materials of this chapter (section 7.1. and 7.2.).

Considering both aspects (i.e., the limited spatial resolution of ESI and spread across participants, and the complex interpretation of a cluster from an fMRI meta-analysis) reveals the complexity of mapping fMRI results to ROIs for ESI analysis. The approach taken in chapter 4 and 5 was selecting the anterior insula and several parts of the inferior frontal gyrus (i.e., pars triangularis and pars opercularis), conducting principal component analysis (PCA) on the time series of the selected ROIs, and using the first principal component for further analysis as the first principal component can be seen as the time series that explains the most variance of the considered time series. This approach thus assumes that the neural activity of the region in Figure 2A is most likely present in nearby ROIs to some degree, and that the variance across the ROIs captured in the first principal component is an adequate representation of said neural activity.

The assumptions of this approach also explain another possible limitation of the experimental studies in chapter 4 and 5: differences in ROI selection between both studies. The two best examples here are the aggregation of the precuneus and PCC from chapter 4 to 5 as it was assumed that both regions were representing neural activity from a single "neural complex" and the different selection of ROIs to represent the anterior insula as it was assumed that the initial selection of ROIs did not adequately represent the cluster identified by Berretz and colleagues (2021). Additionally, the anterior cingulate cortex (ACC) was omitted as a region in

chapter 5 given that it is often subdivided in a dorsal and ventral subsection (Somerville et al., 2006), is mostly linked with the Cyberball (Wang et al., 2017), and the dorsal subsection as the processing center of social exclusion/rejection has been challenged recently (Mwilambwe-Tshilobo & Spreng, 2021). Taken together, the selection of ROIs is a difficult and important step in ESI research, and should be done carefully. Other analysis techniques where no brain atlas is used to divide the dipoles into distinct sets might have been a better approach for the research questions in chapter 4 and 5, and future research should consider these approaches.

The second conceptual limitation of the EEG analysis is the selection of frequency bands, as only the theta, alpha and beta band were investigated. This choice stems from chapter 2, as it was shown that alpha power seemed to be the most consistent frequency band regarding psychosocial stress and although the beta band did not differ significantly in the meta-analysis in chapter 2, a general trend of increased beta power could be identified (Vanhollebeke et al., 2022). The underlying idea for chapter 4 and 5 was that fMRI deactivation patterns would be represented by increased alpha activity, as alpha activity is seen as a representation of inhibitory neural mechanisms (Allen et al., 2004; Jensen & Mazaheri, 2010; Mathewson et al., 2011). fMRI activity increases were subsequently assumed to be (partly) represented by increased beta power, as this frequency band has been linked with attention, sustained cognitive states, and general cortical activity (Engel & Fries, 2010; Miller, 2007; von Stein & Sarnthein, 2000; Wróbel, 2000). This approach has an additional very important advantage: the restriction of frequency bands allows a broader investigation into different ROIs while keeping the amount of statistical tests (i.e., one test for each ROI and frequency band) to a minimum. Research however has shown that fMRI does not directly map to the alpha and beta frequency band, but that this relation is highly complex (Laufs et al., 2006; Pang & Robinson, 2018; Tagliazucchi et al., 2012). Returning to the anterior insulae, it might be possible that the absence of significant findings in chapter 4 and 5 is not related to insufficient spatial precision, but is caused by the fact that the chosen frequency bands simply don't contain the neural activity of interest. One possibility is that the increased anterior insula activity can be found in the gamma band.

Finally it should be mentioned that the specific frequencies that were considered to be the alpha and beta band might have an influence. The EEG spectrum is a continuous entity, so the strict division into specific frequency bands might also affect the final results. It is for example possible that EEG data from participants with a high alpha peak frequency might have falsely inflated beta power values due to this strict separation of frequency bands.

3.1.3. Statistical analysis

Three limitations can be identified regarding the statistical analysis: the lack of individual differences in the analyses, the changes between both experimental studies, and the selection of functional connections to investigate.

The lack of individual differences refers to the fact that the employed statistical analyses did not consider additional variables such as individual differences in self-reported questionnaire scores or physiological activity in the analysis of the EEG results. This was not considered as these measures were mainly collected for the verification of a successful stress induction, but this limits the obtained conclusions to the general sample rather than identifying more refined relationships between the psychophysiological and the neural stress response. Although some individual differences were considered as random intercepts were included in the statistical analysis, the inclusion of the aforementioned variables as well as the inclusion of random slopes (Barr, 2013) would possibly have resulted in more robust results as well as more insights into the complex interactions of the different parts of the stress response.

The changes between both experimental studies refers to the fact that in chapter 4 generalized linear mixed models (GLMMs) were employed, while in chapter 5 only linear mixed models (LMMs) were used. Contrary to LMMs, GLMMs do not assume that the dependent variable is normally distributed. This allows researchers to model the dependent variables with additional distributions such as binomial, gamma, or poisson distributions and thus potentially allows a better fit of the collected data which can be evaluated using the Akaike Information Criterion (AIC). GLMMs were however not employed again in chapter 5 due to the changes it brings to the computation and interpretation of standardized effect sizes (SES). The best known effect size measure is Cohen's D, which can be computed using formula 1 where μ_1 and μ_2 are the means of group 1 and 2 respectively and σ_{pooled} is the pooled standard deviation.

$$D = \frac{\mu_1 - \mu_2}{\sigma_{pooled}} \quad (1)$$

Cohen's D, however, assumes that the data that from which it is computed is normally distributed, and this criterion is not valid if the dependent variable is approximated with other distributions such as the gamma distribution, which was identified as the best distribution to model the EEG data in chapter 4. Therefore the more general description of SES, rather than Cohen's D, was employed to describe the effect sizes found in chapter 4 (Vanhollebeke,

Kappen, et al., 2023). Although theoretically valid, the standard deviation of gamma distributions is formulated differently (Leemis & McQueston, 2008). This subsequently influences the value and interpretation of the obtained SES values. While Cohen's D values are often divided into small ($D < 0.2$), medium ($0.2 < D < 0.7$), or large ($D > 0.8$), this assumption is not correct when SES are computed from non-normal distributions. For an example of the significant influence of the dependent variable distribution on the final SES value, the reader is referred to the supplemental materials of chapter 4 (section 7.6.5.2.). Due to this potential confusion regarding SES values, it was therefore chosen to only employ LMMs in chapter 5. Although this approach has a risk of violation the normality assumption (i.e., non-normal distributions are approximated as normal distributions), it has been argued that this is less problematic as previously thought and that statistical tests are robust to normality violations (Knief & Forstmeier, 2021). Another solution to this problem could be to employ other effect size measures that are robust to non-normal distributions (Li, 2016).

Finally, a reflection is needed upon how functional connections were chosen for investigation. In both chapter 4 and 5, functional connections were chosen based on significant spectral power results. Given that amplitude envelope correlation evaluates changes in amplitude throughout time, it is possible that ROIs whose power changes significantly due to psychosocial stressors also exhibit different functional connectivity. This was done as considering all functional connections results in a high number of needed statistical tests and subsequent more severe multiple comparison correction. Functional connections that were not considered, however, might have revealed further information that was currently not considered.

3.1.4. Physiological analysis

One limitation should be acknowledged regarding the physiological analysis: it is underutilized. Given that the main focus of this dissertation was EEG, physiological data was employed to evaluate the effectiveness of the employed paradigms. This approach is common in neuroimaging research but it limits the conclusions that can be drawn to only the neural stress response. Considering however that the psychosocial stress response is a *bodily* response, it is possible that more insight into the results would have been obtained if physiological data was included in the analysis of the EEG results. This consideration is strenghtened by a recent article (and a growing body of research behind it) that proposes that confining cognition to only the brain is not only limiting, it might simply be incorrect (Ciaunica et al., 2023).

3.2. Limitations of the EEG research field

This section will discuss the limitations that are present in the EEG-psychosocial stress research field in general, and not all limitations necessarily apply to the presented work of this dissertation. Given that this field is less mature than its fMRI counterpart, it is of vital importance that its current limitations are addressed as soon as possible.

The first limitation is the main reason why EEG is less employed than fMRI, and sadly cannot be addressed completely: its lower spatial resolution (Finn et al., 2023). While many advantages in ESI modeling such as realistic FEM models using individual MRI scans (Cuffin, 1996), the incorporation of tissue anisotropy into the head models (Haueisen et al., 2002; Rullmann et al., 2009), or the increased amount of channels (up to 4096 channels in the last year; Papadopoulou et al., 2023) have vastly improved the spatial resolution of ESI estimates, it has as of yet not gained the ability to measure neural activity as precise as fMRI (Finn et al., 2023). The biggest disadvantage regarding spatial resolution for the research subject of this dissertation, however, is the fact that it is not uniform but is a function of distance to the scalp. This makes it impossible for EEG to investigate the involvement of perhaps the most important regions of the psychosocial stress response: the amygdala and hippocampus (McEwen et al., 2016). The absence of these regions in the analysis of the neural psychosocial stress response sadly makes it difficult to understand the exact neural processes that occur throughout the stress phases. It should be mentioned here that attempts have been made to investigate the amygdala using high-density EEG (Damborská et al., 2020) and both experimental and simulation studies have shown that identifying neural activity from subcortical regions is possible (Krishnaswamy et al., 2017; Seeber et al., 2019). These analyses, however, either employ very high electrode density (256 electrodes) combined with individual head models (Seeber et al., 2019) or require sparse activity from cortical regions (Krishnaswamy et al., 2017). The assumption that activity of the amygdala and hippocampus can reliably be detected thus remains a source of debate in the EEG research field and results from these analyses should be considered with caution.

Contrary to the inherent limited spatial resolution, additional limitations are present that can be addressed. The first limitation is, as stated numerously throughout this dissertation, the ubiquity of sensor level analyses for the investigation of psychosocial stress. These analyses are not incorrect necessarily, but given that spectral power in the alpha and beta band are consistently the most evaluated (and significant; Katmah et al., 2021) measures while chapter 4 (Vanhollebeke, Kappen, et al., 2023) and the article by Ehrhardt and colleagues (2021) both

show that these measures are not affected significantly by psychosocial stressors alone, emphasizes the importance of this limitation. The answer to this limitation is not to abandon sensor level analyses, but a more thorough investigation into the driving forces behind the changes in these measures. Additionally, other electrodes should be considered more. As shown in chapter 4, several parietal electrodes did show significant changes in alpha power while this was not found for frontal electrodes (Vanhollebeke, Kappen, et al., 2023).

Another limitation is the high variability in what is considered psychosocial stress. This limitation is most pressing in studies that employ machine learning for the detection of psychosocial stress, as this approach often necessitates a discretization of stress "levels". Examples of this are the articles by Al-Shargie and colleagues (2018) and Subhani and colleagues (2017) that both employ an adaptation of the MIST. Different "levels" of stress, however, are defined by the difficulty of the presented mathematical questions. A similar misconception can be found in the article by Jun and colleagues (2016), where two paradigms are used: the stroop colour-word test (Stroop, 1935) and a mental arithmetic test (without social feedback). In order to obtain different stress "levels", data from the stroop colour-word test are assumed to be a "low stress" while the mental arithmetic test is described as a "high stress". It is clear that differences in cognitive demands are the driving forces for any identified EEG changes, not psychosocial stress. These studies further rely heavily on frontal alpha and beta spectral power features for the classification of these stress levels, so the influence of cognitive demands is even more important to consider (Ehrhardt et al., 2021; Katmah et al., 2021; Vanhollebeke, Kappen, et al., 2023). Of note here is that these articles refer to the detection of "mental stress", not psychosocial stress. Cognitive stressors are a part of mental stressors, so these studies should not be dismissed due to this limitation, yet the ambiguity of what exactly is identified by the obtain ML models remains.

A final limitation is the presence of reverse inference in the field. Similar to the previous limitation, this is most often found in studies employing machine learning (Katmah et al., 2021). The specific way by which reverse inference is present is that differences in EEG measures are taken as proof that different levels of stress are present, as shown in the previous paragraph. The opposite reasoning is also sometimes present. In their review, Katmah and colleagues (2021) discuss a study where the anticipatory and recovery phase of the TSST are compared (Lotfan et al., 2019). Based upon the fact that no difference between both periods is identified in the EEG measure of interest, Katmah and colleagues conclude that these phases "produced the same levels of stress" (Katmah et al., 2021). It is of course possible that both phases were

equally stressful, but this conclusion is not necessarily correct and the absence of EEG differences alone cannot be used as definitive proof for this inference.

3.3. Limitations of the psychosocial stress research field

Considering the psychosocial stress research field as a whole, three final limitations can be identified that are all centered around *how* psychosocial stress is elicited: the overreliance on specific stress paradigms, the subtlety of many stress induction paradigms, and the absence of naturalistic stressor paradigms.

The first limitation is that despite the enormous complexities of social interactions and relations, psychosocial stress is mostly investigated through the employment of a handful of experimental paradigms. This overreliance on a select few paradigms has a simple explanation: these paradigms elicit significant and consistent physiological (e.g., the Trier Social Stress Test (TSST); Kirschbaum et al., 1993) or psychological (e.g., the Cyberball; Williams et al., 2000) changes in the participant population of interest. It becomes thus much more practical to employ a well-known paradigm rather than developing novel paradigms because it allows researchers to delve further into more complex aspects of the psychosocial stress response. This approach has however a significant downside considering neuroimaging, which has been expertly described in a recent article by Muscatell and colleagues (2021): *"Whenever an area of research is over-reliant on a single task, this creates a situation in which we do not have comprehensive understanding of the neural correlates of a broad social experience but rather a more limited knowledge of the neural correlates of a specific task"*. This limitation is critical, and its negative effects have been shown in this dissertation. The co-occurrence of non-social stressors and its influence on frontal alpha and beta power (chapter 2 and 4) and the overreliance on the Cyberball for ERP studies of ostracism (chapter 3) highlight the necessity of novel paradigms to further expand our knowledge of the psychosocial stress response.

The second limitation is the subtlety of many stress induction paradigms, with the best example being the Cyberball. Its underlying psychosocial stressor, ostracism, has been linked with severe effects (see chapter 1, section 1.1.2.), yet the paradigm itself is not capable of consistently eliciting physiological responses commonly associated with the stress response (Helpman et al., 2017; Zöller et al., 2010). There is an obvious ethical limitation to the severity of stress induction paradigms, yet this limitation introduces questions about the external validity of the results obtained from acute laboratory stress induction paradigms.

The final limitation is the absence of naturalistic stressors, which is especially present in neuroimaging-compatible stress induction paradigms. The limitations of neuroimaging almost always necessitate the usage of computer screens to induce stress responses. This however removes perhaps the most important aspect of psychosocial stress: the real-life interactions with other individuals. Considering the employed definition of psychosocial stressors throughout this dissertation (i.e., " *threatening or stressful stimuli arising from social interactions mainly due to their novel, unpredictable or uncontrollable characteristics"*), the absence of real social interactions in itself might severely limit our understanding of the neural psychosocial stress response. The fact that the TSST (Kirschbaum et al., 1993) is capable of reliably eliciting a cortisol response in participants and is therefore considered the "gold standard" is perhaps the best evidence of just how much this limitation limits the neural psychosocial stress research field (Goodman et al., 2017).

Of importance is that the aforementioned limitations do not diminish the enormous progression that has been made regarding the neural psychosocial stress response. It, however, highlights the many complexities that burden the research field and points to avenues for future research to overcome these challenges.

4. Suggestions for future research

The limitations discussed in the previous section can serve as guidelines for future research. This section will first provide suggestions directly related to the current work, and subsequently provide more general suggestions for the research field.

Considering chapter 2, the most pressing matter is a further investigation into the effect of co-occurring stressors on alpha and beta power of frontal electrodes. The article by Ehrhardt and colleagues (2021) has shown that these measures are not sensitive enough for purely psychosocial stressor detection but are instead more likely reflecting cognitive processing, a conclusion strengthened by the experimental study presented in chapter 3, but it is still possible that more potent stressors do in fact affect these measures. Considering that frontal alpha power is the most important feature in machine learning approaches for mental stress detection (Katmah et al., 2021), further clarification of the exact driving forces behind this measure is vital for future research and should be clarified as best as possible.

Considering chapter 3, future research should evaluate more ERP components aside from the P3b within the context of expectancy violations. Given that theories for the CNV (i.e., anticipatory processing; Tecce, 1972), the P2 (i.e., unexpected reward processing; Niedeggen et al., 2014), the N2 (i.e., conflict monitoring; Botvinick et al., 2001; Folstein & Van Petten, 2008), and the P3a (i.e., update of a mental model; Polich, 2007) all imply that an internal model is sustained in the brain that can be assessed through ERP components. It might thus be possible that all these components reflect a similar violation of expectancies (Proulx et al., 2012).

The first suggestions regarding chapter 4 and 5 are directly related to the replication of the identified results. Using counter-balanced designs with larger and more diverse participant populations, the initial results obtained in this dissertation should be verified and solidified so that they can serve as a foundation for future ESI research into the psychosocial stress response. Aside from replication efforts, several extensions to the presented work can be identified. A first extension is the investigation of the anticipatory phase regarding SET (see Figure 1 of this chapter). The anticipatory phase of the TSST (Kirschbaum et al., 1993) would be an excellent candidate for this investigation as it can easily be evaluated within the limitations of EEG measurements. Considering ostracism, returning to the original implementation of the paradigm where a between-subject design with less throws in each condition was employed (Hartgerink et al., 2015; Williams et al., 2000) could be benificial. It might be possible that this implementation is, contrary to the version in chapter 5, capable of inducing a significant psychophysiological stress response, although this approach comes with the disadvantage that ERP components cannot be evaluated. Investigating the anticipatory phase of ostracism might also be possible given that recent research has shown that repeated exposure to the Cyberball still elicits significant behavioral effects in the subjected participant population (Büttner et al., 2023).

As mentioned in section 3.2.3., the integration of physiological data with EEG data is also an important avenue for future research. Two instances can be identified directly in chapter 4 and 5 where this approach could be incorporated. Considering the IBI response analysis in chapter 4 (see chapter 1, section 2.1.2.), it would be interesting to investigate whether the increased sympathetic reactivity is correlated with spectral power of functional connectivity changes of brain regions. Similarly, the immediate physiological response to each individual throw in the Cyberball could be investigated and correlated with ERP components reviewed in chapter 3. It might even be possible that a consistent physiological response is present in this

paradigm that is not identifiable due to the averaging process commonly employed for longer segments of ECG or EDA data.

Aside from suggestions directly related to the work in this dissertation, additional possibilities can be identified that will aid the general field of the neural psychosocial stress response significantly. First and foremost is the increased usage of ESI. As (hopefully) clearly shown in chapter 4 and 5, ESI offers significant advantages compared to sensor level EEG analyses as the extracted measures are more sensitive to psychosocial stressors (shown in chapter 4) and research using ESI can rely on previous fMRI results as a basis for further research (shown in chapter 4 and 5). Although EEG has significantly higher temporal resolution, its full potential has not been achieved within the studies of this dissertation. It is not difficult to imagine just how many novel insights can be obtained by fully exploring the rich temporal structure of the source level EEG time series with dynamic spectral power or functional connectivity analyses. If individual MRI images are obtained in future research, ESI can further resolve the remaining issue regarding the anterior insulae in this dissertation as well as further unravel the complex dynamic neural communication that occurs during and following the presence of a psychosocial stressor. Building upon the initial results of this dissertation, more complex functional connectivity measures can be employed in future scientific endeavours to acquire a more detailed overview of how exactly the many implicated ROIs communicate throughout the different stress response phases and how dysfunctions in these communication pathways result in the debilitating mental disorders that are tightly linked to maladaptive psychosocial stress exposure (Menon, 2011; van Oort et al., 2017).

Another avenue for future research is the usage of novel technological developments such as mobile EEG or virtual reality (VR) as both avenues might overcome a significant limitation currently present in the field: the absence of naturalistic environments (Baumgartner et al., 2006; Lau-Zhu et al., 2019). Although these technologies are still novel, and significant efforts need to be made before they reach their full potential, it is exciting to consider just how much these techniques might add to our current understanding of the stress response. These approaches might also solve the fundamental issue regarding the Cyberball, as it has been shown that more realistic social environments such as the presence of an audience results in much more intense psychological and physiological reactions (Hales et al., 2021; Hartgerink et al., 2015).

A final suggestion is related to the implicit battle between fMRI and EEG. Although clearly stating the advantages and disadvantages of both neuroimaging methods best shows how each modality can address specific challenges in the research field, the assumption that one is better than the other is a naive approach to research and this line of reasoning should be avoided at all times. Both imaging modalities are vital for future research into the psychosocial stress response and the combined collection of data at the same time (i.e., EEG-fMRI studies; Scrivener, 2021; Warbrick, 2022) likely holds the most promise for expanding our understanding into the psychosocial stress response.

5. General conclusions

The primary goals of the presented scientific work in this dissertation were the evaluation of the EEG-psychosocial stress research field and the assessment of ESI as an analysis technique to bridge the research gap between EEG and fMRI studies. In summary, the research presented in this dissertation evaluated the current EEG-psychosocial stress research field in **chapter 2**, the Cyberball-ERP research field in **chapter 3**, and identified potential limitations in both scientific fields. Additionally, in **chapter 4** it was shown that source level EEG measures, obtained through ESI, are sensitive enough to detect neural changes due to only psychosocial stressors without the presence of co-occurring, non-social stressors while more commonly employed sensor level measures were not. **Chapter 5** highlighted the distinct evoked psychosocial stress response that is elicited by specific stressor paradigms. No clearly similar nor clearly distinct changes in any ROI could be identified due to psychosocial stress when EEG data of both paradigms was analyzed together while several spectral power changes, consistent with previous fMRI literature, were found when data from each paradigm was analyzed separately. These studies combined provide a foundation for the further development of the EEG-psychosocial stress research field by both addressing present limitations and identifying opportunities for further development.

The relevance of this scientific work is significant as an increasing interest into the usage of EEG as an affordable method for the detection of psychosocial stress both in a clinical and professional environment can be seen (Giannakakis et al., 2019; Katmah et al., 2021). Considering that the identified complications in chapter 4 and 5 are present in most studies currently published on this topic, the results of this dissertation are highly relevant for the further development of these research lines.

Taken together, the presented studies in this dissertation emphasize the complexities of unraveling the neural psychosocial stress response, the significant influence of how exactly the psychosocial stressors are presented, and the possible misconceptions currently present in the field. Crucially, the scientific work in this dissertation points out the significance of ESI as an analysis method with the potential to bridge the current gap between the EEG and fMRI research lines. This method is likely to significantly contribute to the collective endeavor of better understanding the psychosocial stress response and its influential role in both mental and physical health.

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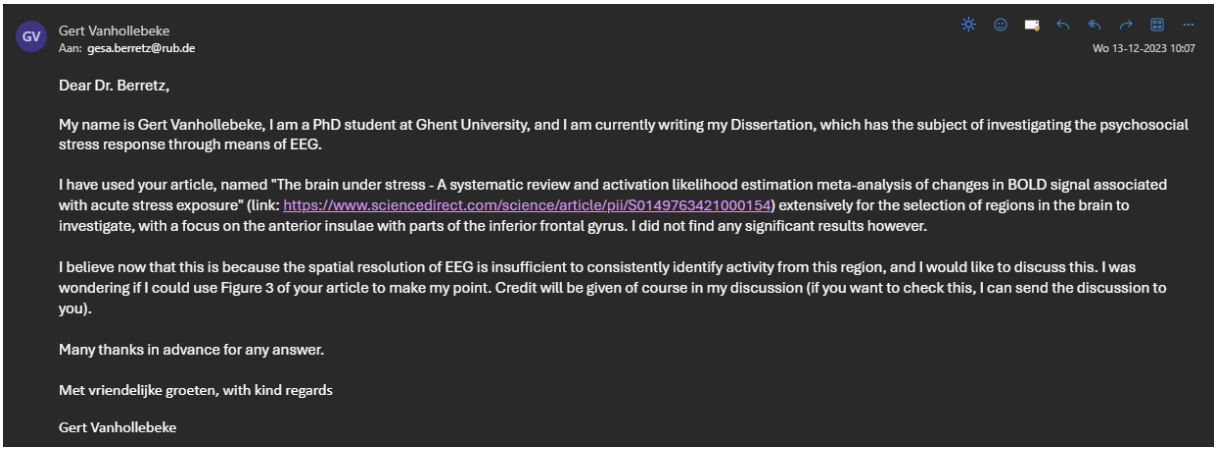

GV Gert Vanhollebeke
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Wo 13-12-2023 10:07

Dear Dr. Berretz,

My name is Gert Vanhollebeke, I am a PhD student at Ghent University, and I am currently writing my Dissertation, which has the subject of investigating the psychosocial stress response through means of EEG.

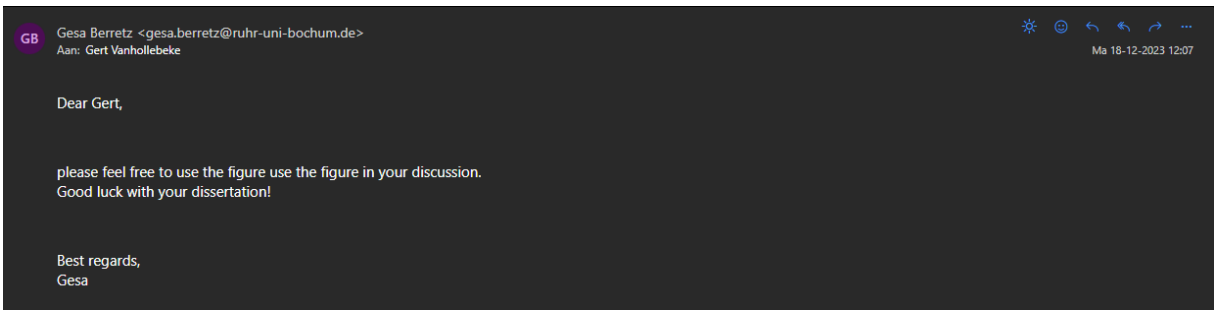
I have used your article, named "The brain under stress - A systematic review and activation likelihood estimation meta-analysis of changes in BOLD signal associated with acute stress exposure" (link: https://www.sciencedirect.com/science/article/pii/S0149763421000154) extensively for the selection of regions in the brain to investigate, with a focus on the anterior insulae with parts of the inferior frontal gyrus. I did not find any significant results however.

I believe now that this is because the spatial resolution of EEG is insufficient to consistently identify activity from this region, and I would like to discuss this. I was wondering if I could use Figure 3 of your article to make my point. Credit will be given of course in my discussion (if you want to check this, I can send the discussion to you).

Many thanks in advance for any answer.

Met vriendelijke groeten, with kind regards

Gert Vanhollebeke



GB Gesa Berretz <gesa.berretz@ruhr-uni-bochum.de>
Aan: Gert Vanhollebeke
Ma 18-12-2023 12:07

Dear Gert,

please feel free to use the figure use the figure in your discussion.
Good luck with your dissertation!

Best regards,
Gesa

Personal Contributions

Chapter 2

Gert Vanhollebeke: Conceptualization, Methodology, Data collection, Data curation, Data analysis, Writing – original draft, Visualization

Stefanie De Smet: Methodology, Data collection, Data curation, Data analysis, Writing – review & editing

Rudi De Raedt: Methodology, Writing – review & editing

Chris Baeken: Methodology, Writing – review & editing

Pieter van Mierlo: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition

Marie-Anne Vanderhasselt: Conceptualization, Resources, Methodology, Writing – review & editing, Supervision, Funding acquisition

Chapter 3

Gert Vanhollebeke: Conceptualization, Methodology, Data collection, Data curation, Data analysis, Writing – original draft, Visualization

Fiebe Aers: Methodology, Data collection, Data curation, Data analysis

Lauren Goethals: Methodology, Data collection, Data curation, Data analysis

Rudi De Raedt: Methodology, Writing – review & editing

Chris Baeken: Methodology, Writing – review & editing

Pieter van Mierlo: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition

Marie-Anne Vanderhasselt: Conceptualization, Resources, Methodology, Writing – review & editing, Supervision, Funding acquisition

Chapter 4

Gert Vanhollebeke: Conceptualization, Methodology, Data collection, Data curation, Data analysis, Writing – original draft, Visualization

Mitchel Kappen: Conceptualization, Methodology, Data collection, Data curation, Data analysis, Writing – review & editing

Rudi De Raedt: Methodology, Writing – review & editing

Chris Baeken: Methodology, Writing – review & editing

Pieter van Mierlo: Conceptualization, Resources, Methodology, Writing – review & editing, Supervision, Funding acquisition

Marie-Anne Vanderhasselt: Conceptualization, Resources, Methodology, Writing – review & editing, Supervision, Funding acquisition

Chapter 5

Gert Vanhollebeke: Conceptualization, Methodology, Data collection, Data curation, Data analysis, Writing – original draft, Visualization

Mitchel Kappen: Data curation, Data analysis, Writing – review & editing, Visualization

Jonas Van Der Donckt: Data curation, Data analysis, Writing – review & editing

Ingemarie Coquyt: Data collection, Data curation, Data analysis

Sofie Van Hoecke: Writing – review & editing

Rudi De Raedt: Methodology, Writing – review & editing

Chris Baeken: Methodology, Writing – review & editing

Pieter van Mierlo: Conceptualization, Resources, Methodology, Writing – review & editing, Supervision, Funding acquisition

Marie-Anne Vanderhasselt: Conceptualization, Resources, Methodology, Writing – review & editing, Supervision, Funding acquisition

Curriculum Vitae

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Education

2019 – Present **Ghent University** - Interdisciplinary doctoral candidate in Medicine and Health Sciences (Psychiatry) & Engineering and Architecture (Biomedical Engineering)

Ghent Experimental Psychiatry (GHEP) Lab
Medical Imaging and Signal Processing (MEDISIP) Lab

Primary advisor: Prof. Dr. Marie-Anne Vanderhasselt
Secondary advisors: Prof. Dr. Ir. Pieter van Mierlo
Prof. Dr. Chris Baeken

2017 – 2019 **Ghent University** – Master of Science – Biomedical Engineering
Magna Cum Laude

2016 – 2017 **Ghent University** – Master of Science – Electronics and ICT Engineering
Magna Cum Laude

2013 – 2016 **Ghent University** – Bachelor of Science – Electronics and ICT Engineering
Cum Fructu

Publications

Vanhollebeke, G., Aers, F., Goethals, L., De Raedt, R., Baeken, C., van Mierlo, P., & Vanderhasselt, M. A. (2023). Uncovering The Underlying Factors of ERP Changes In The Cyberball Paradigm: A Systematic Review Investigating The Impact Of Ostracism And Paradigm Characteristics. *Neuroscience & Biobehavioral Reviews*, 105464.

Li, Z., Pulopulos, M., Allaert, J., De Smet, S., De Wandel, L., Kappen, M., Puttevils, L., Razza, L.B., Schoonjans, E., **Vanhollebeke, G.**, Baeken, C. & Vanderhasselt, M. A. (2023). Vagally-mediated HRV as a marker of trait rumination in healthy individuals? A large cross-sectional analysis. *Psychophysiology*, e14448.

Vanhollebeke, G., Kappen, M., De Raedt, R., Baeken, C., van Mierlo, P., & Vanderhasselt, M. A. (2023). Effects of acute psychosocial stress on source level EEG power and functional connectivity measures. *Scientific Reports*, *13*(1), 8807.

Kappen, M., **Vanhollebeke, G.**, Van Der Donckt, J., Van Hoecke, S., & Vanderhasselt, M. A. (2023). Acoustic and Prosodic Speech Features Reflect Physiological Stress but Not Isolated Negative Affect: A Multi-paradigm Study on Psychosocial Stressors. Under Review, *Scientific Reports.*

Kappen, M., Van Der Donckt, J., **Vanhollebeke, G.**, Allaert, J., Degraeve, V., Madhu, N., ... & Vanderhasselt, M. A. (2022). Acoustic speech features in social comparison: How stress impacts the way you sound. *Scientific Reports*, *12*(1), 22022.

Benschop, L., **Vanhollebeke, G.**, Li, J., Leahy, R. M., Vanderhasselt, M. A., & Baeken, C. (2022). Reduced subgenual cingulate–dorsolateral prefrontal connectivity as an electrophysiological marker for depression. *Scientific Reports*, *12*(1), 16903.

Vanhollebeke, G., De Smet, S., De Raedt, R., Baeken, C., van Mierlo, P., & Vanderhasselt, M. A. (2022). The neural correlates of psychosocial stress: A systematic review and meta-analysis of spectral analysis EEG studies. *Neurobiology of stress*, *18*, 100452.

Conference abstracts

Klooster, D., Puonti, O., **Vanhollebeke, G.**, & Baeken, C. (2023). Using multimodal neuroimaging and electric field simulations to improve TMS targeting. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *16*(1), 188-189.

CW Klooster, D., **Vanhollebeke, G.**, & Baeken, C. (2022). Do electric field simulations have added value for determining TMS coil positions at the scalp for optimal targeting? *Psychiatria Danubina*, *34*(suppl 3), 23-23.

Conference Presentations

June 2022	**Vanhollebeke, G.**, Coquyt, I., Kappen, M., Allaert, J., van Mierlo, P., Vanderhasselt, M. A., Trait rumination is predictive of global network integration of a default mode subnetwork (2022). Organization of Human Brain Mapping.
November 2019	**Vanhollebeke, G.**, Baeken, C., van Mierlo, P., Computer-aided diagnosis of depression in patiens based on resting state fMRI (2019). 18th National Day on Biomedical Engineering

Invited Seminars & Symposiums

April 2022	"Unique challenges for machine learning in the field of psychology and psychiatry: lessons from a neuroimaging perspective." EPP Symposium, Heeze, The Netherlands.
November 2021	"Do's and don't's in machine learning: a neuroimaging example." Machine Learning in Psychiatry for Dummies. Leuven, Belgium.

Service

November 2022	**Co-organizer:** "Psychiatry 2.0.: Towards a new way of thinking" Leuven, Belgium
November 2021	**Co-organizer:** "Machine Learning in Psychiatry for Dummies" Leuven, Belgium

Teaching experience

2020 – 2023 **Supervisor master thesis in Biomedical Engineering (E091103)**

- **"**Can't stop thinking about it? Investigating the brain networks of rumination through means of EEG"
- "Disentangling the heterogeneous clinical responses to transcranial magnetic stimulation based on individual coil positions and induced electric fields"
- "Inferring network architecture through functional connectivity measures: a machine and deep learning approach"
- "Effect of anti-epileptic drugs on functional brain connections"

2020 – 2023 **Supervisor master thesis in Experimental Psychology (H001613)**

- "The modulatory effect of trait rumination on the neural processing of social exclusion: an event-related potential study"
- "Brain networks related to psychosocial stress: an EEG study"
- "The effects of stress on brain-functionality: an EEG study"

2020 – 2023 **Supervisor internship Experimental Psychology (H002007)**

- "Ostracism and the brain: a systematic review and meta-analysis of event-related potentials during the Cyberball game"
- "Self-critical rumination and regret: an EEG resting-state study"
- "Functional connectivity within brain networks due to psychosocial stress based on EEG data"

2020 – 2023 **Teacher course Neuro-Engineering Science (E010382)**

- Teaching practical sessions DTI and Functional Connectivity

Research skills

Programming	MATLAB (signal processing), Python (signal processing, machine learning), R (statistical analysis)
Software	Brainvision Analyzer, Brainstorm, OpenSesame, E-Prime
Hands-on experience	EEG data collection, Physiological data collection (EDA, ECG), behavioral tasks

References

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