DECODING COMPLEXITY:

A DATA-DRIVEN APPROACH TO UNRAVELING TRANSDIAGNOSTIC MARKERS IN PSYCHIATRY

Hannah Meijs

DECODING COMPLEXITY:

A data-driven approach to unraveling transdiagnostic markers in psychiatry

Hannah Meijs

The work described in this doctoral dissertation was carried out at Stichting Brainclinics Foundation, in collaboration with Maastricht University.

Meijs, Hannah
Decoding complexity:
A data-driven approach to unraveling
transdiagnostic markers in psychiatry

Published by Brainclinics Insights,
Nijmegen, The Netherlands

DECODING COMPLEXITY:

A data-driven approach to unraveling
transdiagnostic markers in psychiatry

DECODEREN VAN COMPLEXITEIT:
Een datagedreven benadering om
transdiagnostische markers in de psychiatrie
te ontrafelen.

DISSERTATION

to obtain
the degree of Doctor at Maastricht University,
on the authority of the Rector Magnificus,
Prof. Dr. Pamela Habibovic,
in accordance with the decision of the Board of Deans,
to be defended in public on
Tuesday, the 18th of June 2024, at 10:00 hrs.

by

Hannah Meijs
born on the 1st of August 1990
in Maastricht, The Netherlands

Supervisor
Prof. dr. A.T. Sack

Co-supervisors
Dr. M. Arns,
Maastricht University/
Brainclinics Foundation, Nijmegen
Dr. J. J. Luykx,
Amsterdam UMC/
GGZ InGeest

Assessment Committee
Prof. dr. B.M. Jansma (Chair)
Maastricht University
Prof. dr. B. Rutten
Maastricht University
Prof. dr. med. S. Olbrich,
The University of Zurich, Switzerland
Dr. D. Smit,
Amsterdam UMC, Amsterdam, the Netherlands

Cover and layout: Mark Koppenberg, Velp
ISBN-978-90-830013-4-0

TABLE OF CONTENTS

Chapter 1	General introduction	9
Chapter 2	A polygenic-informed approach to a predictive EEG signature empowers antidepressant treatment prediction: A proof-of-concept study	31
Chapter 3	A posterior-alpha ageing network is differentially associated with anti-depressant effects of venlafaxine and rTMS	61
Chapter 4	A deep learning derived transdiagnostic EEG signature indexing hypoarousal and impulse control: Implications for treatment prediction in ADHD and MDD	93
Chapter 5	General discussion	123
References		143
English Summary		163
Nederlandse samenvatting		167
Impact Paragraph		171
Curriculum Vitae		175
List of Publications		178
Conference Contribution and other Presentations		179
Dankwoord		181

1

GENERAL INTRODUCTION

In this thesis, we study the intersection of current psychiatric clinical practice and personalized psychiatry, delving into the potential of stratified psychiatry to enhance treatment outcomes. By investigating the role of potential biomarkers, including genetic factors and brain activity, through the utilization of large datasets and innovative methodologies, we aim to uncover insights that could revolutionize psychiatric care.

LIMITATIONS OF CURRENT CLINICAL PRACTICE AND ALTERNATIVES

In current clinical practice, the Diagnostic and Statistical Manual of Mental Disorders (DSM; version 5 (APA 2013) at the time of writing) is widely used in the field of psychiatry to categorize and define psychiatric disorders based on symptoms and functional impairment, providing a standardized framework for diagnosis and treatment. It was first published by the American Psychiatric Association in 1952 as an initiative to develop practical, standardized diagnostic criteria,

and it has undergone several revisions since then reflecting advancements in the understanding of mental health conditions (Surís, Holliday, and North 2016). Nevertheless, these classifications, conceptualized prior to modern neuroscience and based on observable signs and symptoms, lack consistent predictability for treatment response and may not fully encompass the fundamental underlying mechanisms of dysfunction associated with a specific disorder (Insel et al. 2010; Morris and Cuthbert 2012; Surís, Holliday, and North 2016). Furthermore, psychiatric disorders often co-occur, which is attributed to symptom heterogeneity within diagnoses and symptom overlap between diagnoses (Taylor et al. 2023), paving the way for a transdiagnostic approach.

TRADITIONAL TREATMENT APPROACHES

Traditionally, treatment decisions have relied on a 'diagnosis-informed one-size-fits-all' approach, involving the prescription of standardized medications and the application of established therapeutic techniques, often following a 'stepped care' model (Arns et al. 2022). In stepped care, psychiatric patients undergo interventions matched to their needs, starting with low-intensity, low-cost and easily accessible treatments with fewest side effects, and progressing to more specialized, higher-intensity interventions with generally higher side effect profiles (Van Straten et al. 2010). While this model, like the DSM-5, provides a structured framework, it may not adequately address the heterogeneity and complex nature of mental health conditions, potentially leading to suboptimal outcomes.

For major depressive disorder (MDD), also known as depression, there is only limited evidence to suggest that stepped care should be the dominant treatment model (Firth, Barkham, and Kellett 2015; Van Straten et al. 2014). Moreover, under the stepped care model, remission rates for depression stand at around 30% to 40% following the initial treatment attempt, gradually decreasing with each subsequent attempt, and approximately one-third does not achieve remission even after four sequential treatment steps (Rush et al. 2006). Thus, there is a pressing need to enhance remission rates in depression.

TRANSDIAGNOSTIC PSYCHIATRY

Transdiagnostic approaches in psychiatry focus on common underlying factors and processes that are shared across different psychiatric conditions, rather than exclusively adhering to the categories and boundaries set by conventional classification systems. This approach has potential benefits, such as simplifying treatment protocols, developing interventions that are effective across a range of psychiatric disorders, reducing overlap in therapeutic techniques, and promoting a more unified understanding of psychiatric disorders (Barlow et al. 2017). Therefore, this thesis aims to explore the feasibility of implementing a transdiagnostic approach in clinical practice, with a focus on uncovering common underlying factors or transdiagnostic markers that are associated with treatment outcomes in psychiatry.

MDD AND ADHD: AN OVERVIEW

This thesis focuses primarily on MDD, with a secondary emphasis on attention deficit/hyperactivity disorder (ADHD). Hence, a brief overview of these psychiatric conditions follows.

MAJOR DEPRESSIVE DISORDER

MDD is a common psychiatric disorder characterized by a multifaceted origin, typically conceptualized through a biopsychosocial framework that recognizes the significance of various biological, psychological, and social factors as key contributors to the disorder (Freedman 1995). The model contributes to the understanding of the heterogenous clinical presentation and symptomatology of depression (Rush 2007). However, according to the DSM-5 (APA 2013), MDD is characterized by the presence of at least five out of nine symptoms during the same two-week period, representing a change from previous functioning. These symptoms include at least depressed mood most of the day, nearly every day and/or a markedly diminished interest or pleasure in all, or almost all, activities. Treatment options include, among others, psychotherapy, pharmacotherapy and transcranial magnetic stimulation (TMS). TMS is a noninva-

sive treatment that involves the application of a magnetic field that passes through the scalp and skull, to electrically stimulate neurons in the underlying human cerebral cortex, beneath the coil (Wassermann and Lisanby 2001). While single pulses of TMS result in complex but brief responses, repeated pulses can induce more sustained effects on brain activity, potentially leading to lasting modifications in cortical excitability (Ridding and Rothwell 2007).

ATTENTION DEFICIT/HYPERACTIVITY DISORDER

ADHD is a common psychiatric disorder that often co-occurs with other psychiatric conditions such as depressive disorder (Choi et al. 2022). ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with daily functioning or development. Unlike MDD, it is a neurodevelopmental disorder with childhood onset that may change in manifestation with development from preschool through adult life (Zuddas et al. 2000). To meet ADHD DSM-5 criteria, sufficient symptoms must be present before the age of 12, and they must cause significant impairment in functioning. It is estimated that the prevalence of ADHD is around 5% in children and adolescents, with a significant portion continuing to experience symptoms into adulthood (Polanczyk et al. 2007). ADHD can be treated through different approaches, including pharmacological interventions like psychostimulants (e.g. methylphenidate), as well as behavioral strategies involving various psychosocial interventions (Zuddas et al. 2000).

Although impulsivity is recognized as a symptom of ADHD, a study conducted by Crips & Grant revealed that a wide range of psychiatric conditions exhibit heightened impulsivity (Crisp and Grant 2024). This suggests impulsivity could signify a shared process across different psychiatric disorders, evidenced by the high co-occurrence of ADHD and other conditions like personality disorder and substance use disorder (Trull et al. 2000; Bornovalova et al. 2005; Weiner, Perroud, and Weibel 2019; Katzman et al. 2017). These findings hint at the benefit of considering impulsivity as a transdiagnostic factor applicable to a wide spectrum of psychiatric conditions (Crisp and Grant 2024; Koudys et al. 2023).

CRITIQUE OF SUBJECTIVE ASSESSMENT TOOLS

Self-reported or clinician-administered surveys, like the Hamilton Rating Scale for Depression (HAM-D), are tools for assessing the severity at baseline and progression of symptoms, monitoring treatment progress, and providing supplementary information for diagnostic purposes. Drawbacks of such questionnaires include their subjective nature and the possibility of response bias, meaning that individuals provide inaccurate or misleading responses to questions, which can stem from various reasons, like social desirability (answering to appear socially acceptable) (Furnham 1986). In the International Study to Predict Optimized Treatment for Depression (iSPOT-D), for example, there was only a 59% agreement between the HAM-D and self-rated Quick Inventory of Depressive Symptomatology (QIDS) for remission (defined as HAM-D score ≤ 7 or QIDS score ≤ 5).

The HAM-D, which has long been considered the gold standard severity rating questionnaire for MDD, has a poor interrater and retest reliability on item level and assesses a concept of depression that only partially aligns with the operationalization of depression outlined in the DSM-5 (Bagby et al. 2004). Furthermore, some studies have indicated that the alignment between neurobiology and (subjective) psychological measures is limited (Krepel et al. 2019; Van der Vinne et al. 2017; Saveanu et al. 2015). Therefore, we adopted biological (first two studies) and neuropsychological measures (last study) in this thesis, to facilitate a shift away from relying solely on subjective assessments prone to bias, toward utilizing objective data less susceptible to individual interpretation for prognostic purposes.

ROLE OF GENETICS IN AS OBJECTIVE MARKER GUIDING PSYCHIATRIC TREATMENT

Genetic liability is an area of research interest in biomarker-guided psychiatric treatment, where objective genetic information is utilized to choose the most effective treatment. Given the highly polygenic nature of many psychiatric disorders, such as MDD and ADHD, no single genetic variant has reliable predictive capacities (Kember et al. 2021). On

the other hand, specific genetic variants are associated with a range of psychiatric disorders (Smoller et al. 2013). Many different common genetic variations, distributed throughout an individual's genome, have been associated with a specific trait or disease by multiple genome-wide association studies (GWAS) (Uffelmann et al. 2021). These variants can be combined to calculate an individual score that assess the overall genetic loading for a specific trait or disease; a polygenic risk score (PRS) (Lewis and Vassos 2020). Calculating the PRS (or polygenic score, PGS) involves a weighted summing of the number of trait-associated alleles, carried by an individual at each variant. Utilizing polygenic scores allows for predicting individual traits or the predisposition to a particular disease, independent of environmental influences.

However, a review by Wray et al. concluded that, in clinical practice, PRS/PGS on their own have limitations in accurately predicting future diagnoses and treatment outcome of common complex conditions (Wray et al. 2021). Nevertheless, while polygenic scores fall short of yielding definitive predictions, they could offer support as adjuncts to other predictive methodologies, potentially aiding in stratification and guiding clinical decision-making.

Pharmacogenomic studies have focused on genetic biomarkers of antidepressant treatment response in MDD, resulting in a PRS (or PGS) of antidepressant response (PRS-AR) (Pain et al. 2020). The usefulness of PRS-AR was validated by Lin et al. in an independent dataset that was not part of the initial GWAS (Lin et al. 2022). In the first two studies included in this thesis (chapter 2 and 3), we have used the PRS-AR as an intermediate step for the selection of brain networks that likely have a biological basis.

TRANSITING TO PRECISION PSYCHIATRY THROUGH STRATIFIED PSYCHIATRY

In recent years, there has been a growing recognition of the need for a more nuanced understanding of psychiatric disorders in order to provide more tailored and personalized therapeutic approaches and interventions, acknowledging the unique characteristics and needs of each individual.

CONCEPT OF PERSONALIZED MEDICINE

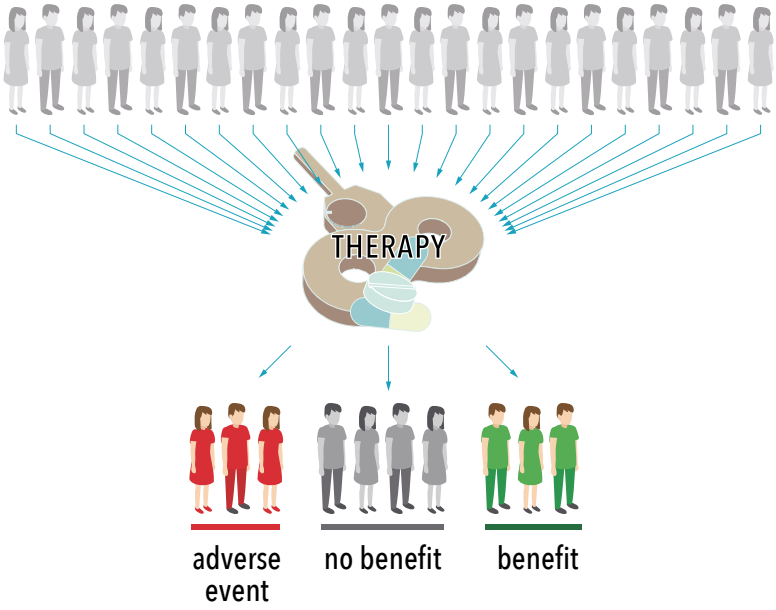
Personalized medicine, also known as precision psychiatry, aims to improve the diagnosis and treatment of disorders by employing biomarkers that enable effectiveness in the initial treatment phase (Vieta 2015). Those biomarkers should accurately represent heterogenous groups, taking into account the interindividual variance. In this thesis, large and heterogenous cohorts of psychiatric patients were employed to uncover potential biomarkers. The first study (chapter 2) utilized a dataset comprising more than 1,000 adult patients, predominantly in-hospital, diagnosed with a variety of psychiatric disorders (including MDD, psychotic disorder, and substance use disorder, among others). In the last two studies (chapter 3 and 4), we analyzed a dataset containing over 4,000 subjects diagnosed with a range of psychiatric conditions (including MDD, ADHD, and obsessive-compulsive disorder, among others), outpatient and spanning various clinical stages of life.

STRATIFIED APPROACH AS A STEP-UP TO PRECISION PSYCHIATRY

Despite the increasing attention to precision psychiatry, the manner in which clinicians diagnose and manage psychiatric disorders – guided by average efficacy, side-effect rates and personal experience – has remained largely unchanged for decades (Arns et al. 2022). While recent research has focused on biomarkers and precision psychiatry, so called 'stratified psychiatry' could be a more practical alternative for individuals with mental health conditions (Arns, Olbrich, and Sack 2023). Stratified psychiatry involves subgrouping patients with comparable biomarker profiles to improve the likelihood of a clinical response or remission to established treatments, as outlined by Arns et al. (Arns et al. 2022). Thus, it does not claim to provide the optimal treatment for each person, but rather is a pivotal step towards precision psychiatry (figure 1).

Patients can be stratified based on biological, genetic, and clinical factors, in line with the postulated biopsychosocial model that underlies the heterogeneity of MDD. It is evident that a single marker fulfilling all criteria for aiding diagnosis and predicting treatment across different neuropsychiatric disorders does not exist. Achieving this goal of precision psychiatry will likely involve combining a range of biomarkers, and initiating biomarker-guided treatment decisions,

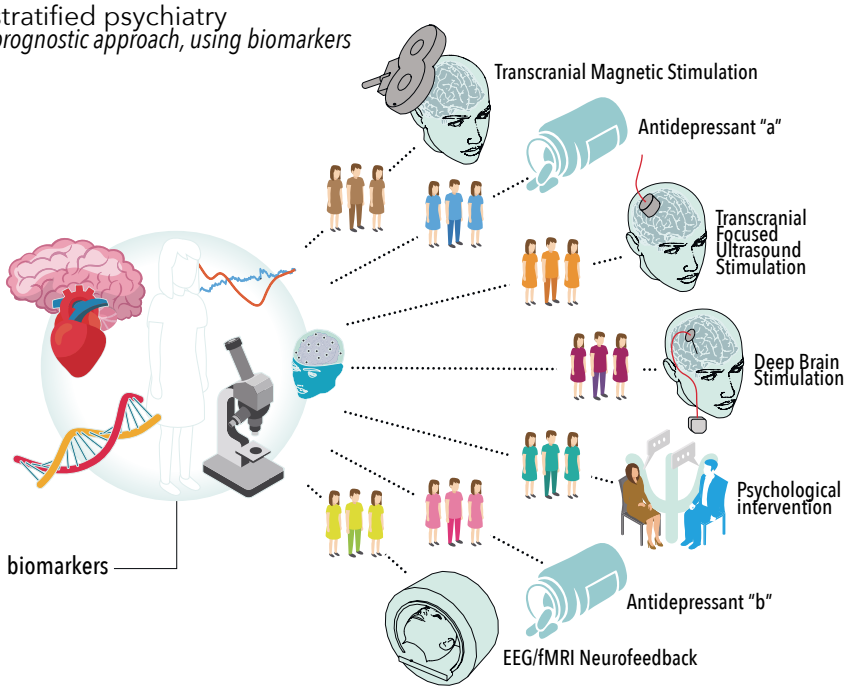
which in turn may result in higher remission rates compared to treatment as usual (Olbrich, Dinteren, and Arns 2016). Therefore, our thesis focuses on stratifying psychiatric patients based on objective, biologically grounded markers to offer optimized treatment, aiming to increase the likelihood of remission.



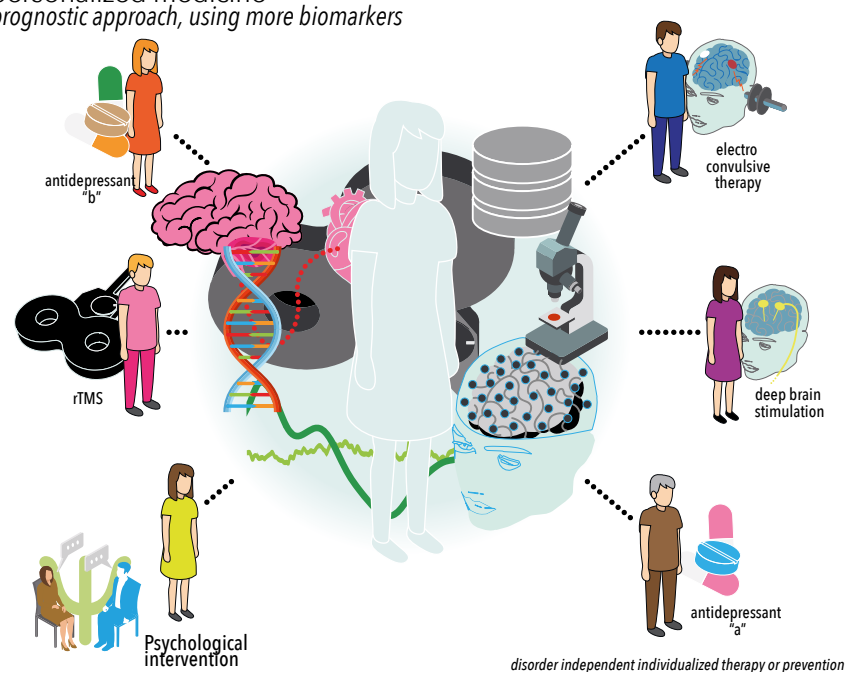
one-size-fits-all psychiatry - *diagnostic approach, no biomarkers*

Figure 1. *The infographic compares the current 'diagnosis-informed one-size-fits-all' approach (above) with the prognostic models of stratified psychiatry (opposite page, top) and precision psychiatry (opposite page, bottom). Precision psychiatry entails treating psychiatric patients according to a personalized profile that is based on objective markers (including neuroimaging and genetics, among others), to address the unique characteristics of each patient and optimize clinical outcomes. Stratified psychiatry involves subtyping patients with similar biomarker profiles to improve the likelihood of clinical response to established treatments.*

stratified psychiatry
prognostic approach, using biomarkers



personalized medicine
prognostic approach, using more biomarkers



disorder independent individualized therapy or prevention

RESEARCH DOMAIN CRITERIA (RDOC) FRAMEWORK

The National Institute of Mental Health (NIMH) has developed the Research Domain Criteria (RDoC), offering a framework that aims to advance the understanding of mental health by emphasizing a dimensional and neuroscientific approach, encouraging scientists to explore the underlying genetic, biological and psychological factors underlying behavior, across multiple domains (Insel et al. 2010; Morris and Cuthbert 2012). The statement goal of the NIMH is to develop, for research purposes and eventually for clinical use, new ways of classifying mental conditions based on dimensions of observable behavior and neurobiological measures (Cuthbert and Insel 2013). These dimensions embody constructs that symbolize evolving knowledge related to brain organization and functioning, shaped by ongoing research progress (Morris and Cuthbert 2012; Cuthbert and Insel 2013). Dimensions are further categorized under five overarching domains of function (for example the arousal/regulatory domain), which reflect a conceptual typology. By incorporating the RDoC framework, there is potential to redefine the classification of psychiatric disorders, which could be based on objective biological or neuropsychological measurements, as well as observable behavior dimensions. Such reclassification may pave the way for improved treatment outcomes through a stratified or more personalized approach. Ultimately, this approach reflects our evolving understanding of brain organization and functioning. We harnessed the RDoC approach to delve deeper into the regulatory systems, with further elaboration to follow.

UNCOVERING BIOMARKERS WITH NEUROIMAGING TECHNIQUES

Neuroimaging techniques, including magnetic resonance imaging (MRI) and electroencephalography (EEG) are methods to gain more insights in brain organization and functioning, and have proven to be valuable methods for the identification of biological predictors of TMS for depression (Klooster et al. 2023). Moreover, structural and functional MRI shows potential in improving treatment outcomes in

MDD for other treatment modalities (e.g. pharmacotherapy), as outlined in a review by Fonseka et al. (Fonseka, MacQueen, and Kennedy 2018). A study utilizing functional MRI (fMRI) on a large multisite sample employed a data-driven data-reduction technique distinguishing subtypes of depression beyond existing diagnostic boundaries and exhibiting predictive capabilities for TMS responsiveness (Drysdale et al. 2017). We embraced a data-driven data-reduction technique in this thesis, although MRI was not employed as part of that technique.

EEG AS ALTERNATIVE TO MRI

An alternative approach to MRI for examining brain function and subtyping psychiatric disorders, based on extensive data from large samples, is by using resting-state EEG (figure 2A-C). This is a non-invasive neuroimaging technique that provides insights into the electrical human brain activity (Berger 1929). EEG has several advantages compared to MRI, as it is more cost-efficient and broadly available, with a high temporal resolution, albeit low spatial resolution. EEG uses a set of electrodes strategically placed along the scalp, for example according the International 10-20 system (Klem et al. 1999). A spontaneous EEG represents the postsynaptic potentials of (thousands to millions) cortical pyramidal neurons firing in synchrony, making the signal large enough to be conducted through the skull and recorded at the scalp (Schomer and Silva 2011).
By capturing the fluctuations in voltage over time, EEG allows researchers and clinicians to observe and analyze brain wave patterns. EEG signals are often categorized into distinct frequency bands, such as delta (0.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), beta (14-30 Hz), and gamma (above 30 Hz) (Silva 2013), each associated with specific cognitive and sensory processes (Başar et al. 2001). The alpha rhythm, for example, occurs during relaxed wakefulness and is particularly prominent when the eyes are closed, mainly over the parieto-occipital cortex (Silva 1991). In this thesis, we utilized EEG to identify objectively measurable transdiagnostic markers for treatment prediction and stratification purposes.

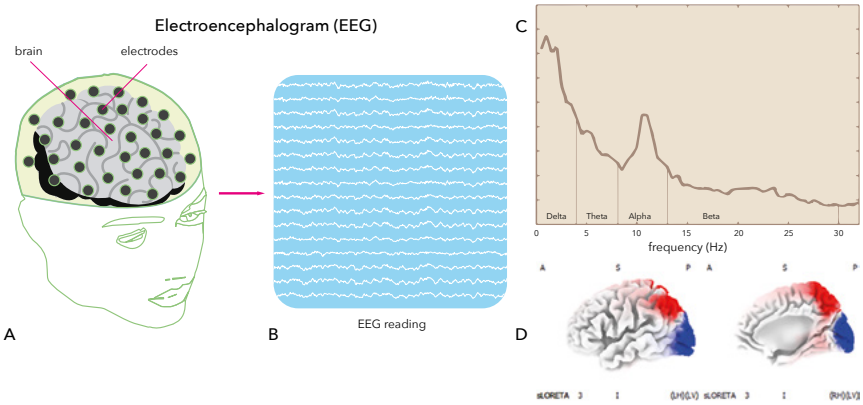


Figure 2. Electroencephalography (EEG) is a non-invasive technique used to record electrical brain activity by placing electrodes on the scalp, which detect signals generated by neurons firing in the brain (A). These recordings appear as brain waves (B) categorized into different frequency bands (delta, theta, alpha, beta, and gamma waves), depicted in the time domain (C). Through power spectral analysis, EEG data is transformed into the frequency domain, revealing power distribution across frequency bands. Source localization analysis identifies specific brain regions responsible for generating EEG signals (D). This process reconstructs neural sources in three dimensions, offering insights into the spatial distribution of brain activity.

POTENTIAL OF EEG IN STRATIFIED PSYCHIATRY

In clinical settings, EEG has since long served as a valuable diagnostic tool to assess and monitor various neurological conditions, like epilepsy (Gibbs, Davis, and Lennox 1935). EEG plays an emerging role for understanding how EEG signatures or patterns correlate with specific psychiatric disorders and holds promise for enhancing diagnostic precision and treatment response in psychiatry (Hughes and John 1999).

For MDD and ADHD, several EEG parameters were found to be of discriminative and predictive value: specific patterns or abnormalities in the EEG are associated with treatment outcomes in a manner that depends on factors (e.g. sex/gender or the specific treatment used) (Arns, Gordon, and Boutros 2017; Arns et al. 2016; Olbrich and Arns 2013; Wu et al. 2020; Roelofs et al. 2020). These include, among others, EEG vigilance-based markers and several quantitative EEG markers, especially within the alpha and theta range, like frontal alpha asymmetry (FAA) (Olbrich, Dinteren, and Arns 2016; Olbrich and Arns 2013) and individual alpha peak frequency (iAPF) (Voetterl et al.

2023; Voetterl et al. 2022). FAA has been thoroughly investigated as a potential prognostic biomarker in MDD, and is defined by greater alpha power over left than right frontal region, which is indicative of relatively less left frontal activation and greater right frontal activation (Bruder et al. 1997). It is a stable trait that predicts treatment response irrespective of moment of measurement and use of medication, and promising to optimize MDD treatments (Van der Vinne et al. 2019).
Nevertheless, while some EEG markers show promise for clinical applications, they have not been implemented in clinical settings to date; there is a need for replication and validation in out-of-sample scenarios (Widge et al. 2019). However, the iAPF, which refers to the dominant frequency of alpha oscillations in an individual (Haegens et al. 2014), is recently replicated and validated by Voetterl et al. (Voetterl et al. 2023), and ready to be implemented in clinical practice as a transdiagnostic treatment stratification EEG biomarker that can successfully assign patient subgroups to various ADHD and MDD treatments.

LORETA: UNLOCKING BRAIN NETWORKS FOR TREATMENT PREDICTION

Although EEG is a promising neuroimaging technique for clinical applications, fMRI is the prevailing technique for functional imaging of the human brain. This imaging method measures and maps brain activity by detecting changes in blood flow and oxygenation, producing three-dimensional (3D) images (Turner et al. 1998). EEG lacks adequate information regarding the 3D distribution of electric neuronal activity; it has low spatial resolution. The process of reconstructing the location and distribution of electric potentials based on EEG measurements is termed 'inverse problem' (Jatoi et al. 2014). Many possible solutions of this problem exist, and low-resolution brain electromagnetic tomography (LORETA) is one of them (figure 2D).
LORETA is an often used and essential tool in this thesis. It is a functional imaging method that uses EEG measurements for estimating the cortical source distribution of electric neuronal activity by a lin-

ear inverse solution method that identifies maximum synchronization in orientation and strength among neighboring neuronal populations (Roberto D. Pascual-Marqui et al. 2011; R. D. Pascual-Marqui et al. 2002). It models the cortex as a set of volume elements (voxels) within a digitized atlas, yielding a 3D depiction of electric neuronal activity across specified frequency bands. The LORETA method has undergone prior utilization and validation with human data, and its most recent version, called exact LORETA (eLORETA), has an ability to achieve correct localization even when structured noise is present (Aoki et al. 2015). Thus, computations by eLORETA convert sensor EEG data into spectral density 3D images within a solution space comprising 6239 voxels.

FUNCTIONAL BRAIN NETWORKS DERIVED THROUGH LORETA

Through the application of eLORETA, one can acquire independent, spectral-spatial components (or functional networks) via independent component analysis (ICA) applied to the voxel domain and across frequencies. ICA (or functional ICA; fICA) is a computational method that aims to find a set of independent signals (components) that, when linearly combined, constitute the observed data (Comon 1994). The fundamental assumption in ICA is that the observed signals result from mixtures of statistically independent source signals. The technique works by maximizing the statistical independence among the estimated components. Thus, this represents a data-driven, data-reduction technique, as it minimizes the input data without losing information.

The functional networks derived from eLORETA represent sets of brain regions that consistently and simultaneously activate or deactivate within and across a specified frequency band. Consequently, independent cross-frequency spectral-spatial functional networks are established. Using this approach, a study by Gerrits et al. successfully identified both the default mode network (active at rest) and task-positive network (active during goal-directed tasks) in a large sample, that was also out-of-sample validated in an ADHD sample (Gerrits et al. 2019). In this thesis, the eLORETA-fICA method allowed us to compute various functional brain networks from EEG data. These networks were tested for their potential to serve as biomarkers with predictive capabilities for treatment outcomes.

INTEGRATING FUNCTIONAL BRAIN NETWORKS WITH GENETICS

In the first two studies (chapter 2 and 3) of this thesis, we embraced an integrative approach by combining polygenic factors associated with treatment (non)response (assessable through PRS) with neurobiological factors represented by EEG signatures. This comprehensive strategy appears promising for effectively predicting therapeutic outcomes. This novel strategy we employed involves utilizing PRS-AR to guide the selection of functional brain networks for subsequent prediction of antidepressant treatment response in MDD. Thus, a biologically plausible network linked to a polygenic liability for antidepressant response is chosen and subsequently validated in an independent dataset consisting of patients with MDD that receive a specific (evidence-based) treatment. The functional network may be useful as a clinical tool to stratify patients to antidepressant treatments, thereby enhancing chances of initial remission, thus limiting the relative inefficiency of the current stepped care approach and alleviate the burden and duration of the disease.

TRANSDIAGNOSTIC EEG MARKER FOR HYPOAROUSAL

Beta spindles entail synchronized EEG activity within the beta frequency range, centered around a specific frequency. Spindling excessive beta (SEB) in particular is characterized by fast beta waves with a "spindle morphology with an anterior emphasis" (Johnstone, Gunkelman, and Lunt 2005). The identification of this EEG signature in the frontocentral lobes, relies on visual examination.

Spindle activity in the alpha and slow beta frequency range is best studied and commonly appears during superficial and non-rapid eye movement stages of sleep (known as sleep spindles) and under certain medicines, such as barbiturates (Johnson et al. 2012; Silva 1991). While sleep spindles are linked to learning and memory (Johnson et al. 2012), the function of SEB is not clear. Beta activity is generally associated with hyperarousal and alertness, and increased levels of beta activity are found in patients experiencing insomnia (Perlis et al. 2001). Furthermore, beta activity rarely occurs in children and adolescents and should not exceed 25 μV in amplitude (Clarke et al. 2001c).

SEB AS A TRANSDIAGNOSTIC MARKER FOR HYPOAROUSAL

Since sleep spindles occur during drowsiness and sleep, SEB might be indicative of hypoarousal. In this context, SEB has been explored as a potential transdiagnostic marker within the arousal/regulatory domain of the RDoC, and it is associated with impulse control (Arns, Swatzyna, et al. 2015; Krepel et al. 2021).

Various psychiatric disorders manifest heightened impulsivity, highlighting the relevance of conceptualizing impulse control as a transdiagnostic factor across a spectrum of psychiatric conditions (Crisp and Grant 2024). Within the ADHD population, where impulsivity stands as one of the key symptoms according to the DSM-5, prevalence rates of (spindling) excess beta (described as beta levels exceeding two standard deviations above the mean of the control group, or three within each subgroup, depending upon the study) in the EEG range from 13% to 20% (Clarke et al. 2001c; Chabot and Serfontein 1996; Clarke et al. 1998; 2001b). Notably, research conducted by Arns et al. (Arns et al. 2008) revealed comparable prevalence of frontocentral beta spindles between individuals with ADHD and healthy controls. Moreover, results from a study by Clarke et al. indicated that ADHD children exhibiting excess beta activity are not hyperaroused (Clarke et al. 2013). These findings suggest that the presence of excess beta or beta spindles can be regarded as a neurophysiological 'normal variant' that is not associated with hyperarousal, but represents a distinct subgroup within the ADHD population that responds well to stimulant medication (Chabot et al. 1999; Clarke et al. 2003). In this thesis, we investigated the ability of SEB to predict treatment outcomes in ADHD, as well as MDD, considering that impulsivity occurs in various psychiatric conditions.

APPLICATIONS OF DEEP LEARNING

Artificial intelligence, particularly the swiftly advancing field of deep learning, stands out as a promising novel approach towards personalized and improved treatment as it can help predict disease and treatment outcomes. Deep learning, a subfield of machine learning that concentrates on artificial neural networks, especially deep neural networks, enables computer models with multiple layers to comprehend complex and large data at various levels of abstraction (LeCun, Bengio, and Hinton 2015). A recent study from Van Putten

et al. (Putten, Olbrich, and Arns 2018), which has been replicated (Bučková et al. 2020), demonstrated that a deep neural network can accurately predict sex from EEG data. This finding reveals that brain rhythms exhibit sex-specific patterns and underscores the capability of deep neural networks to identify features in spatiotemporal data that might go unnoticed through visual assessment. Therefore, deep learning seems valuable in automating EEG biomarkers reliant on visual inspection. Since SEB is an EEG signature that is dependent on visual inspection and therefore subjective, we trained a convolutional neural network (a type of artificial neural network) deep learning model to classify SEB in the EEGs of nearly 200 subjects, which were annotated visually by an EEG expert.

TRIANGULAR RELATIONSHIP BETWEEN SLEEP, SEB AND IMPULSE CONTROL

A study examining the relation between sleep maintenance, SEB and impulse control hypothesized that frontal SEB could be considered a transdiagnostic state marker indicating impulse control problems stemming from sleep-related problems (Arns, Swatzyna, et al. 2015). Links between sleep and impulsivity have been studied. The regulation of sleep, arousal, affect, and attention overlaps, and effects of sleep deprivation encompass changes at the level of prefrontal cortex (PFC) integration across these regulatory systems (Dahl 1996). Poor sleep quality is thus related to cognitive and emotional impairments, like diminished attentional and behavioral control (as observed in ADHD), and regulation of emotions (as observed in depression) (Dahl 1996; Harrison and Horne 2000). Moreover, the association between sleep and impulsive behavior seems bidirectional (Bauducco, Salihovic, and Boersma 2019). Therefore, we delved into the triangular relationship of sleep maintenance problems in relation to impulse control on one hand and SEB on the other. We investigated the potential of SEB as transdiagnostic marker for impulsivity or hypoarousal, as well as its capacity to predict treatment outcomes.

THESIS CHAPTERS OVERVIEW

In the second chapter, a proof-of-concept study is described. Here, we demonstrate a polygenic-informed EEG data-driven, data-reduction approach to predict treatment outcome in MDD. To that end, we conducted eLORETA-fICA in a large dataset of over 1,000 patients, producing functional brain networks. We used PRS-AR to guide the selection of functional brain networks for subsequent response prediction, thus combining genetics with neurophysiology approaches. In the third chapter, the follow-up study is presented that builds upon the previous one. Here, we demonstrate an analysis flow that was inspired by the previous study, aiming to identify a functional brain network capable of predicting remission to MDD treatments. The eLORETA-fICA was applied to a lifespan database consisting of more than 4,000 psychiatric patients, to better capture functional brain networks across the lifespan. The remainder of the study was of explorative and descriptive nature. In the fourth chapter we explored EEG frontal beta activity (frontocentral beta power and SEB classified using a deep learning algorithm) as a potential transdiagnostic biomarker linked to impulsivity and sleep problems, both objectively measured. Furthermore, we demonstrate that SEB classified by deep learning, has both diagnostic and predictive capabilities. In summary, the results underscore the significance of the RDoC approach in uncovering biomarkers within psychiatric research.
In conclusion, in this doctoral thesis we strive to pave the way for personalized psychiatry through stratified approaches to treatment. By integrating methodologies such as neuroimaging, genetics, and deep learning, we aim to transcend the limitations of traditional diagnostic frameworks and offer new insights that hold promise of revolutionizing psychiatric care.

2

A POLYGENIC-INFORMED APPROACH TO A PREDICTIVE EEG SIGNATURE EMPOWERS ANTIDEPRESSANT TREATMENT PREDICTION: A PROOF-OF-CONCEPT STUDY

ABSTRACT

The treatment of major depressive disorder (MDD) is hampered by low chances of treatment response in each treatment step, which is partly due to a lack of firmly established outcome-predictive biomarkers. Here, we hypothesize that polygenic-informed EEG signatures may help predict antidepressant treatment response. Using a polygenic-informed electroencephalography (EEG) data-driven, data-reduction approach, we identify a brain network in a large cohort (N = 1,123), and discover it is sex-specifically (male patients, N = 617) associated with polygenic risk score (PRS) of antidepressant response. Subsequently, we demonstrate in three independent datasets the utility of the network in predicting response to antidepressant medication (male, N = 232) as well as repetitive transcranial magnetic stimulation (rTMS) and concurrent psychotherapy (male, N = 95). This network significantly improves a treatment response prediction model with age and baseline severity data (area under the curve, AUC = 0.623 for medication; AUC = 0.719 for rTMS). A predictive model for MDD patients, aimed at increasing the likelihood of being a responder to antidepressants or rTMS and concurrent psychotherapy based on only this network, yields a positive predictive value (PPV) of 69% for medication and 77% for rTMS. Finally, blinded out-of-sample valida-

tion of the network as predictor for psychotherapy response in another independent dataset (male, N = 50) results in a within-subsample response rate of 50% (improvement of 56%). Overall, the findings provide a first proof-of-concept of a combined genetic and neurophysiological approach in the search for clinically-relevant biomarkers in psychiatric disorders, and should encourage researchers to incorporate genetic information, such as PRS, in their search for clinically relevant neuroimaging biomarkers.

INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder with a complex etiology that is generally explained from a biopsychosocial model, in which multiple biological, psychological, and social factors are all considered important contributors (Amare, Schubert, and Baune 2017). Furthermore, genetic risk factors of MDD overlap with other psychiatric disorders and specific genetic variants are in turn associated with a range of psychiatric disorders (Smoller et al. 2013). It is assumed that the multifactorial model for MDD (partly) underlies its heterogeneous symptomatology and variable treatment efficacy (Belmaker and Agam 2008; Rush 2007). In line with the biological heterogeneity of MDD that in turn may be related to this variable treatment outcome, pharmacogenomic studies have focused on genetic biomarkers of antidepressant treatment response in MDD. Genome wide association studies (GWASs) have identified genetic variants associated with antidepressant efficacy and SNP-based heritability of antidepressant response significantly differs from zero (Pain et al. 2020), but clinically-relevant and converging loci have remained elusive (Ising et al. 2009; Garriock et al. 2010; Li et al. 2020; Uher et al. 2010; Fabbri et al. 2018; Ji et al. 2013; Li et al. 2016; Tansey et al. 2012). Thus, antidepressant treatment outcome is likely a complex trait and explained by several loci of small effect (Hodgson et al. 2012), with recent evidence indeed suggesting that antidepressant response is polygenic (Pain et al. 2020). Consequently, a polygenic instead of single gene or locus approach, by calculation of the individual's polygenic risk score (PRS), seems valuable to associate genetic risk

with treatment (non)response (Fabbri et al. 2020). At present however, evidence for reliable out-of-sample prediction of MDD treatment response is limited (García-Gonzáleza et al. 2017; Ward et al. 2018; Foo et al. 2019; Li et al. 2020; Pain et al. 2020; Fanelli et al. 2020; 2022). A proposed strategy to effectively predict therapeutic outcomes for clinically prognostic purposes, is to integrate PRS with other predictors, such as neuroimaging and clinical characteristics (Amare, Schubert, and Baune 2017).

Electroencephalography (EEG) is a non-invasive neuroimaging technique to quantitatively analyze oscillatory brain activity of neurons with high temporal resolution (Silva 2013). EEG biomarker research for treatment prediction in MDD has shown that certain EEG patterns or abnormalities are differentially associated with drug-specific or drug-class specific antidepressant treatment effects (Arns, Gordon, and Boutros 2017; Arns et al. 2016; Olbrich and Arns 2013) as well as rTMS outcome (Arns et al. 2014; Erguzel et al. 2014; Hasanzadeh, Mohebbi, and Rostami 2019; Roelofs et al. 2020). Such studies have also demonstrated qualitative sex differences in topographic distribution of EEG activity and sex-specific predictors of treatment response of alpha asymmetry (Arns et al. 2016), EEG connectivity (Iseger et al. 2017) and event-related potentials (Dinteren et al. 2015). Until recently, consensus was that the use of EEG for clinical decision making is not justified (Widge et al. 2019). However, two recent studies using machine-learning approaches applied to resting-state EEG features identified predictive signatures for sertraline, a selective serotonin-reuptake inhibitor, that related differentially to rTMS response (Wu et al. 2020; Zhang et al. 2020). This finding is of clinical relevance as it suggests that EEG signatures may be useful as a clinical tool to stratify patients to one of two evidence-based antidepressant treatments (rTMS vs. antidepressant medication), empowering initial treatment response rates (Michel and Pascual-Leone 2020).

Our primary aim was to demonstrate proof-of-principle for the use of a polygenic-informed EEG data-driven, data-reduction approach to predict treatment outcome in MDD. To that end, we conducted a functional independent component analysis (fICA) using LORETA (Low Resolution Brain Electromagnetic Tomography), producing independent spectral-spatial components (i.e. functional brain networks), in a large dataset. In a prior study, this fICA method was tested and vali-

dated (Gerrits et al. 2019; Aoki et al. 2015) and demonstrated to reliably identify the default mode network (DMN) and task-positive network (TP) in a sample of 1,397 subjects, which was also replicated in an independent ADHD sample (Gerrits et al. 2019). We used PRS-AR (Pain et al. 2020) to guide the selection of functional brain networks for subsequent response prediction, thus combining genetics with neurophysiology approaches. The usefulness of PRS-AR was recently validated in an independent dataset of pharmacotherapy response, that was not included in the original GWAS (Lin et al. 2022). Here, we show one functional network that is significantly associated with polygenic liability to antidepressant response in men. Then, in subsequent translational analyses, we demonstrate how this EEG signature is associated with response to antidepressant medication as well as rTMS and concurrent psychotherapy in male MDD patients in an independent dataset. Finally, we analyzed the prediction accuracy of treatment response in male MDD patients based on the discovered EEG signature.

MATERIALS AND METHODS

PARTICIPANTS AND PRS CALCULATION, DATASET 1

The first dataset was used for functional independent component analysis (fICA). EEG recordings of participants were collected from September 2013 until September 2018 at Ziekenhuis Netwerk Antwerpen (ZNA), a large community hospital in Antwerp, Belgium. The study was approved by the Institutional Review Board of ZNA. We abided by the principles of the Declaration of Helsinki. A total of 1,195 adult participants – 1,132 psychiatric patients with various (predominantly mood, psychotic and/or substance use) disorders and 63 healthy controls to obtain a heterogenous sample – were included and provided written informed consent. Exclusion criteria for all participants were age <18 years, inability to give informed consent for whatever reason, and restlessness that could interfere with the EEG. Healthy controls were defined as having no current psychiatric episode and never been treated by a mental health service. After preprocessing, the total sample for fICA consisted of 1,123 (1,061 patients and 62 healthy controls). We aimed to use the largest sample possible for a data-driven-data-reduction into fICA components that would be transdiagnostic and ex-

plain most of the variance, rather the relying on a too narrow dataset of MDD patients only. In earlier work we also demonstrated this for Brainmarker-I. When we developed this Brainmarker on a large heterogenous dataset, it translated better to a normative dataset, instead of the other way around (Voetterl et al. 2022).
Additionally, DNA was extracted from the 887 participants of the total sample providing written informed consent for genetic analyses. Standard stringent genotype and subject-level quality control (QC) and principal component analysis were carried out with PLINK 1.9 (S. Purcell et al. 2007) to obtain a genetic homogenous cohort, and PRSs were calculated as per standard procedures using PRSice2 (Choi and O'Reilly 2019). DNA QC and PRS calculation details, and references to the GWASs used for PRS generation can be found in Supplementary Materials and Methods.

PARTICIPANTS OF THE MEDICATION STUDY, DATASET 2

The second dataset used for translational purposes and the evaluation of treatment effects was an international multi-center, randomized, prospective open-label trial (phase-IV clinical trial): iSPOT-D sample (International Study to Predict Optimized Treatment in Depression). This study consisted of 1,008 patients diagnosed with non-psychotic MDD who were randomized to escitalopram, sertraline, or venlafaxine. All participants provided written informed consent and this study was approved by the institutional review boards at all of the participating sites and this trial was registered with ClinicalTrials.gov under id NCT00693849. At baseline and after 8 weeks of treatment patients filled in the Quick Inventory of Depressive Symptomatology (QIDS). Only data from participants who completed 8 weeks of randomized medication treatment ('per protocol' sample) were included. Details about this sample have been published elsewhere (Arns, Etkin, et al. 2015; Arns et al. 2016).

PARTICIPANTS OF THE RTMS STUDY, DATASET 3

The third dataset was used for translational and discovery purposes and the evaluation of treatment effects. It consisted of 196 patients,

diagnosed with non-psychotic MDD or dysthymia and Beck Depression Inventory version 2 (BDI-II) score ≥ 14 at baseline, who underwent protocolized rTMS treatment concurrent with psychotherapy. All participants provided written informed consent. Participants received high-frequency TMS (10 Hz left dorsolateral prefrontal cortex, DLPFC) or low-frequency TMS (1 Hz right DLPFC); a minority received both 1 Hz and 10 Hz sequentially. All patients completed at least 10 sessions of treatment, and filled in the BDI-II at baseline and at the last session (on average session 21). Details about this sample are described elsewhere (Donse et al. 2017; Krepel et al. 2019).

PARTICIPANTS OF THE PSYCHOTHERAPY STUDY, DATASET 4

The third dataset, used to investigate if the EEG component was also predictive for psychotherapy without concurrent rTMS treatment, included patients diagnosed with non-psychotic MDD or dysthymia and BDI-II ≥ 14 at baseline who received any form of psychotherapy as monotherapy (N = 175). Of these patients, 94 underwent cognitive behavior therapy (CBT) and 81 underwent another form of psychotherapy. BDI-II baseline was recorded at intake, and again at the end of psychotherapy treatment. All participants provided written informed consent.

EEG RECORDINGS AND PREPROCESSING

Resting-state eyes closed EEG recordings (see Supplementary Materials and Methods) were acquired from 65 channels of the Electrical Geodesics Incorporated (EGI; Magstim, UK) system (dataset 1) and from 26 channels (10-20 electrode international system of the Neuroscan NuAmps (Compumedics, Australia; other datasets).

Subsequently, the following steps were taken in the EEG preprocessing and artefact rejection procedure using Brain Vision Analyzer 2.0 (Brain Products, Germany): 1) data filtering: 0.5-90 Hz (dataset 1) or 0.3-100 Hz (dataset 2 and 3), and notch filter; 2) removal and spherical spline interpolation of noisy signals or flat lines; 3) electro-oculography (EOG) correction, using a regression-based technique (Gratton, Coles, and Donchin 1983); 4) segmentation in 4-second epochs; and

4) artefact-rejection using an automatic procedure (criteria: maximal allowed difference of 150 μV peak-to-peak). This resulted in a minimum of one-minute data per subject.

LORETA-FICA MODEL

The EEG was used for estimating the cortical source distribution of electric neuronal activity by means of LORETA (free academic software available at https://www.uzh.ch/keyinst/loreta). This method weights minimum norm inverse solution, and localization inference is based on the standardized estimates of the current density (Roberto D. Pascual-Marqui et al. 2011).
The following analysis steps were performed using the collection of 4-second artefact-free epochs obtained from dataset 1. In the first step, each EEG recording was transformed to the frequency domain, using the discrete Fourier transform. The cross-spectral matrices were obtained for six frequency bands, defined as: delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), beta (14.5-30 Hz), low-gamma (31-47 Hz), and high-gamma (>70 Hz). Aiming to eliminate the notch bands used at different sites in the EU and US, the 48-69 Hz range was excluded. In the second step, from data of each cross-spectrum matrix, the spectral density was computed for each cortical voxel, sampled at 5 mm resolution in a realistic head model, using the MNI152 template (Aoki et al. 2015). In the third step, the spectral-spatial data of all subjects was concatenated, and ICA (see Supplementary Materials and Methods) was performed on these data, aiming to identifying independent spectral-spatial components (i.e. functional networks). This method was recently validated in Aoki et al. and Gerrits et al. and reliably identified DMN (default mode network) and TP (task-positive) networks (Aoki et al. 2015; Gerrits et al. 2019).

INDEPENDENT COMPONENTS

Each independent cross-frequency spectral-spatial functional network (fICA network or EEG component) represents sets of brain regions that are consistently activated or deactivated together within and across a given frequency band. The number of EEG components here was esti-

mated from a dimensionality measure related to Wackermann's Omega Complexity (Wackermann 1996).
To visualize the functional networks (i.e. correlation of brain regions that are consistently activated or deactivated), a threshold at 3 z-values was set. Individual scores per fICA network were obtained for each subject, corresponding to the strength of that network for a given individual subject.
The functional networks that were established based on the first dataset, were prospectively applied to dataset 2 and 3. Likewise, for each subject in each dataset, EEG component scores were obtained per network. These were used in the statistical analysis.

OUTCOME MEASURES

For component selection (discovery, figure 1), the independent EEG components were regressed on PRS-AR (dataset 1, see section 'Statistics' below). For the prediction analysis, first we focused on dimensional improvement of depressive symptoms, and then on categorical improvement (response, defined as ≥ 50% reduction of baseline score) to confirm the robustness of previous findings (translation, figure 1). Outcomes were based on the QIDS or BDI-II (dataset 2 and 3).

STATISTICS

SPSS version 27 was used for statistical analyses. Effects sizes (ES) of significant main effects are reported as explained variance (R^2) and/or standardized beta (β) for continuous measures or as Cohen's d (*d*) for binary measures. Two-sided tests were performed for statistical significance testing.
In order to accommodate potential sex-specific interaction effects, sex was included as main factor, or – in case the analysis could not accommodate sex as main factor – women and men were analyzed separately, rather than handled as covariate since covariation can only resolve quantitative (not qualitative) sex differences. Previous iSPOT-D studies

reported sex-specific predictors of treatment outcome (Dinteren et al. 2015; Arns, Etkin, et al. 2015; Arns et al. 2016; Iseger et al. 2017), so this would enable us to identify potential biomarkers. If no sex interaction was found, or the effect for both sexes was in the same direction (and for PRS analysis at $p<0.01$), analyses were performed on men and women combined, otherwise separately.

The analysis procedure that was performed in this study is visualized in figure 1. First, a discovery analysis examined if there was an association between one or more fICA components and PRS-AR (dataset 1). To that end, a linear regression analysis, controlling for age and the first five genetic ancestry principal components (PCs), was run between individual EEG component strength (measured by individual scores that present how active the network is in an individual) and 11 PRS-AR p-value thresholds ($P_T = 5.0\times10^{-6}$ to $P_T = 1$) in order to choose the optimal P_T, which is unknown a priori (Choi, Mak, and O'Reilly 2020). The significance level was conservatively corrected for multiple outcomes and sex-specific subgroup analysis: $\alpha = 0.05/(29$ [EEG components] $\times$ 2 [male vs female participants]) = 0.00086. The EEG component that showed significant associations with PRS-AR was selected for subsequent analyses.

Second, a translational analysis was performed (dataset 2 and 3) to examine if the selected EEG component was predictive of treatment outcome. The significance level for these translational follow-up analyses was set at conventional $\alpha= 0.05$ as these analyses were intended for translation of the findings in the discovery analysis. We investigated possible associations between individual EEG component strenght and absolute changes in BDI-II and QIDS score. The absolute change (Δ) was defined as the symptom severity score difference between baseline and treatment completion. Therefore, ΔBDI-II and ΔQIDS were regressed on the individuals EEG component strength, adding age as covariate. Factorial ANCOVAs were run to investigate if the individual EEG component scores were significantly different in responsive patients compared to nonresponders. Response and sex were added as fixed factors; age was added as covariate in all models. For both categorical as well as continuous outcome analyses an additional analysis with baseline severity score was done.

Subsequently, to assess the predictive value of the EEG component, a discriminant analysis on treatment outcome was performed. Prior

studies had already tested several psychological (personality, anxiety etc.), demographic and behavioral measures and their ability to predict remission or response in these samples, and failed to find robust and clinically relevant predictors (Krepel et al. 2019; Saveanu et al. 2015; Arns et al. 2016). The basic predictive model consisted of age and baseline severity. Then we tested whether the model performance improved when the EEG component, detected in the discovery analysis, was added as predictor ('improved model'). The positive predictive value (PPV) was calculated for the improved model. Also, a receiver operating characteristic (ROC) curve was plotted.

The optimal network score cut-off points for medication and rTMS during psychotherapy were determined by calculating the maximum Youden Index (J), which measures the accuracy of a dichotomous diagnostic test, for the prediction of response to increase effectiveness of the EEG component (as single predictor) as a potential biomarker. Based on these cut-offs, prediction models were built to evaluate the clinical utility of the EEG component for prediction purposes, by calculating the PPV (i.e. within-subsample response rate) and improvement of the response rate relative to the observed response rate in a crosstabulation.

Finally, a blinded out-of-sample validation was performed in male MDD patients receiving psychotherapy (dataset 4); response status was predicted based on the previously determined cut-off for rTMS with concurrent psychotherapy. Subsequently, the PPV and negative predictive value (NPV) were calculated in a crosstabulation including all male patients. A sensitivity analysis consisting of the subgroups CBT versus other psychotherapy was also performed.

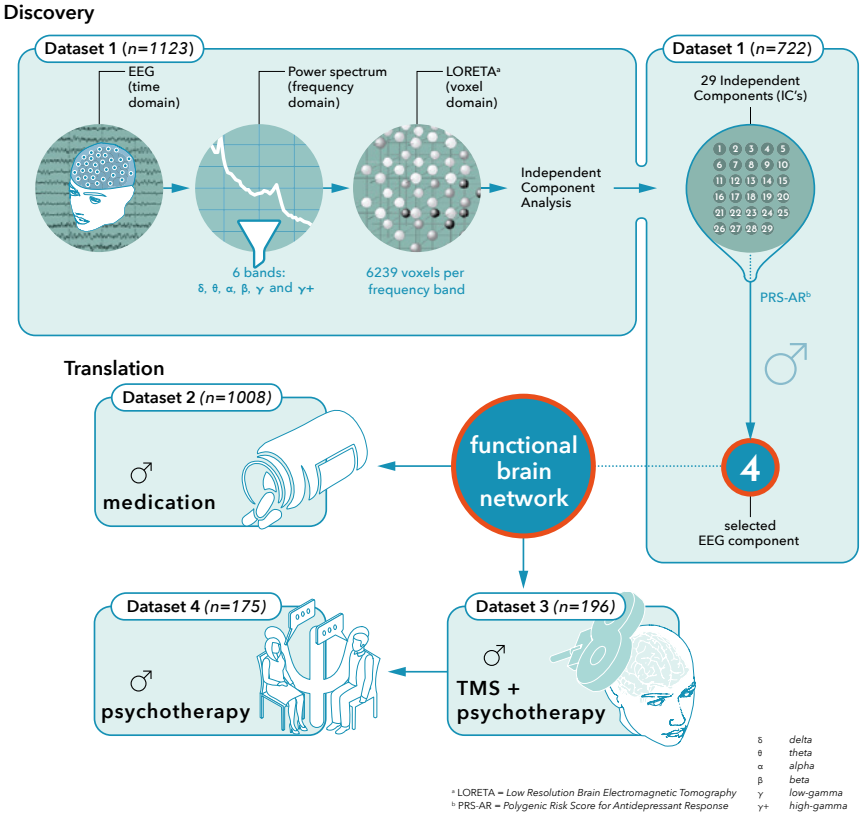


Figure 1. Chart depicting the study set-up and analysis pipeline. The LORETA-fICA method was used in the discovery analysis. Data for this method consisted of 6 a priori defined frequency bands and 6239 voxels (6x6239) per subject (dataset 1). This resulted in 29 independent cross-frequency spectral-spatial components. In male participants, only fICA EEG component 4 was found to be robustly associated with PRS-antidepressant response (PRS-AR). No association was found in women. EEG component 4 was used for translational and discovery purposes in two independent datasets: MDD patients randomly prescribed antidepressants (escitalopram, sertraline or venlafaxine; dataset 2) and treated with rTMS and concurrent psychotherapy (dataset 3). Network activity of fICA EEG component 4 was significantly associated with treatment response in male, and – in the other direction (but not significant) – in female MDD patients. In another independent dataset (dataset 3), consisting of patients who underwent psychotherapy, the network is found to be predictive of treatment response.

RESULTS

An overview of the baseline demographic characteristics and response and remission rates per dataset after EEG preprocessing can be found in Table 1.

	Dataset 1: 'discovery'	Dataset 3: medication	Dataset 2: rTMS + PT	Dataset 3: psychotherapy
Totoal number participants	1,195	1,008	196	175
N included in study	1,123[1]	535	193	141
Ratio men/women	617/506	245/290	95/98	50/91
Mean age (SD), years	40.3 (13.2)	38.5 (12.6)	43.3 (12.8)	37.2 (13.8)
Mean baseline score (SD)	BDI-II; 31.1 (12.1)	QIDS; 14.5 (3.7)	BDI-II; 31.2 (10.1)	BDI-II; 31.5 (9.3)
Response rate (%)	N/A[2]	48.8	66.3	32.6

Table 1. Baseline characteristics *Abbreviations: rTMS = repetitive transcranial magnetic stimulation; PT = psychotherapy; QIDS = Quick Inventory of Depressive Symptomatology; BDI-II = Beck Inventory Index, version 2.*

[1] N = 1,123 subjects included in EEG statistical analyses (cleaned EEG data available), with N = 722 (also cleaned DNA data available) included in subsequent PRS (polygenic risk score) analyses.

[2] N/A as this was a non-intervention study no treatment effects were assessed.

DISCOVERY ANALYSIS IDENTIFIES 29 COMPONENTS USING LORETA-FICA (DATASET 1)

Of the 1,195 participants enrolled in dataset 1, the final sample for the LORETA-fICA analysis after quality control (see Materials and Methods) consisted of 1,061 hospital-admitted psychiatric patients (most were diagnosed with MDD, schizophrenia and/or substance use disorder) and 62 controls (N = 1,123; dataset 1). The appropriate dimensionality of the data was established using sphericity test which indicated 29.0 dimensions; hence the LORETA-fICA analysis was constrained to 29 components, accumulatively explaining 97.0% of the total variance in EEG power (see figure 1: discovery).

RELATING COMPONENTS TO POLYGENIC RISK

Of the 1,123 participants, PRS association analysis was performed using the data of 722 participants remaining after EEG pre-process-

ing and genetic quality control (QC; see Table S1 for all QC steps). Among 29 outcomes and two sex-specific datasets, PRS-AR was associated with the individual fICA EEG component 4 score, after controlling for age and the first five PCs ($\beta = 0.172$; $R^2 = 2.91\%$; optimal $P_T < 0.3$) at $p = 0.000567$ in male participants. This EEG component was used for translational analysis. The PRS model fit of the association between fICA EEG component 4 and PRS-AR was indicative of high polygenicity (see figure 2).

Figure 3 shows fICA EEG component 4 (this component explains 0.78% of the total EEG variance), representing joint deactivation and activation of neural activities coming from sets of regions that form functional spatial-spectral networks. Most prominent are delta and theta power seen at the DLPFC, inversely correlated with delta power in the right anterior PFC. Also, delta – and to a lesser extent theta – activity is evident in somatosensory-motor cortices. Occipital activity is present within frequencies ranging from the delta (most prominent) to beta band.

The individual EEG component 4 scores only correlated with some non-EEG related baseline characteristics in women, not in men.

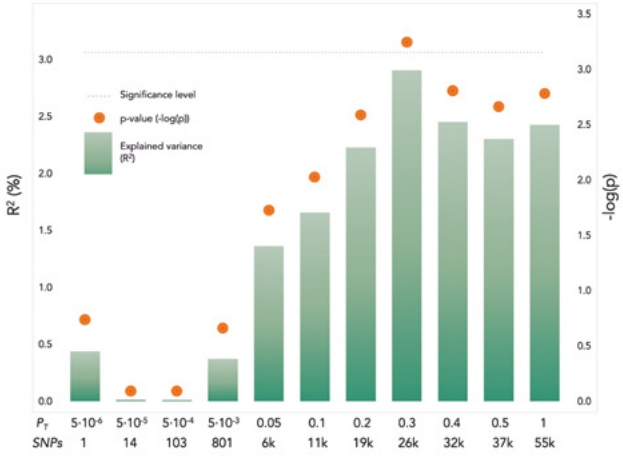


Figure 2. Polygenic risk regression model of antidepressant response in men using different p-value thresholds. The graphs show the explained variance (R^2 as %) of EEG component 4 in men by PRS-AR (polygenic risk score of antidepressant response [improvement]; blue bars), and the corresponding p-value (presented as -log; orange dot) on the x-axis per p-value threshold (P_T) on the y-axis. The Bonferroni-corrected significance level is also presented (α, grey dotted line). Note that, in general, the more lenient the P_T is, the more variance is explained by the PRS (and the closer to significance its p-value is), indicating the EEG component is highly polygenic.

TRANSLATION AND DISCOVERY ANALYSIS IN AN INDEPENDENT TREATMENT RESPONSE DATASET (DATASET 2 AND 3)

The primary outcome for translational analysis (see figure 1: translation) was dimensional improvement of depressive symptoms and secondary was categorical response (defined as ≥50% reduction of baseline score), based on the BDI-II at baseline and after rTMS. Data were normally distributed.

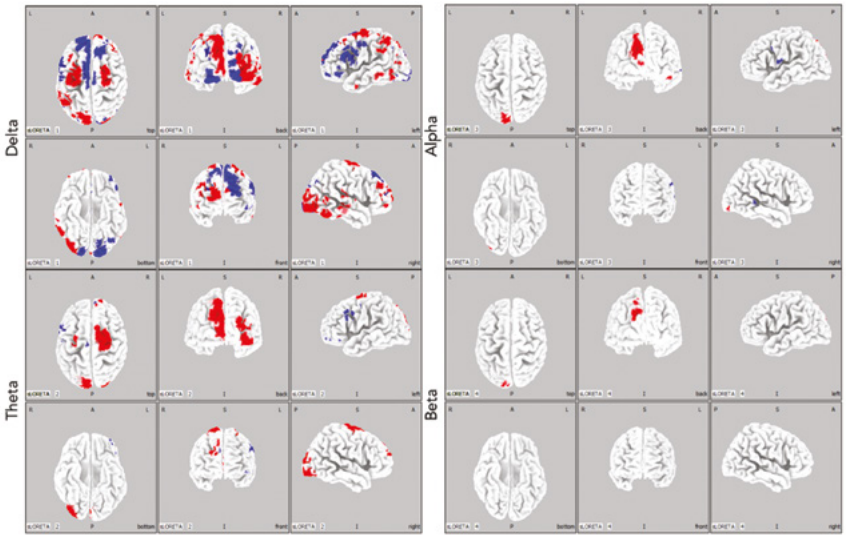


Figure 3. Functional network of the component obtained with LORETA-ICA. Map of the EEG functional network obtained in this study using LORETA-ICA (independent component 4). The colors represent correlated and inversely correlated EEG power changes of brain regions (when neural activity in red colored regions inceases, activity in blue colored regions decreases). The component covers activity in different parts of the brain, predominantly within the delta and theta frequency bands, and minimally within the alpha and beta frequency bands. Delta band: frontally (mainly Brodmann area [BA] 6 and 8 to 10), occipitally (mainly BA 17 to 19), parietally (mainly BA 7 and 40), and temporally (mainly BA 21 and 37). Theta band: frontally (mainly BA 6 and 9), occipitally (BA 17 to 19), and parietally (BA 7 and 19). Alpha band: occipitally (BA 17 to 19) and partietally (mainly BA 7 and 19). Beta band: occipitally (BA 19)

RELATING THE PRS-INFORMED EEG COMPONENTS TO ANTIDEPRESSANT MEDICATION OUTCOME (DATASET 2)

Of the 1,008 (dataset 3) participants, data of 535 were included for translational analysis (treated per protocol, sufficient clean EEG and all channels available).
First, linear regression analysis of ΔQIDS on individual EEG component score with age as covariate yielded an R^2 of 2.3% (β = -0.153; p = 0.019) in men, and R^2 of 1.7 % (β = -0.131; p = 0.021) when baseline QIDS score was added as covariate. The association in women (with age as covariate) was found to be in the other direction, but was not significant (R^2 = 0.125%; β = 0.035; p = 0.563).
Second, to examine categorical outcomes, an ANCOVA with EEG component score as dependent variable and response, sex and treatment arm as fixed factors, and age as covariate yielded a significant ($p < 0.05$) interaction of response × sex, but no interactions with treatment arm. Repeating this analysis in men and women separately yielded a main effect for male patients (d = 0.358, F = 7.168, p = 0.008), but no effect for women. Adding baseline QIDS (F = 6.795; p = 0.010) as additional covariate confirmed these results.

Based on the results of the previous analyses, a discriminant analysis was performed on men only and an ROC curve plotted (see figure 4A). This showed that age and baseline QIDS did not significantly predict medication response (Wilk's Lambda, λ = 0.981; Chi-Square, χ^2 = 4.320; p = 0.115), but adding the EEG component to the model significantly improved response prediction (λ = 0.953; χ^2 = 11.021; p = 0.012) with a PPV of 63% and area under the curve (AUC) of 0.623 (p = 0.001; 95%-confidence interval, CI = [0.551-0.694]). A sensitivity analysis with the EEG component as the only predictor confirmed that the component significantly contributed to medication response prediction (λ = 0.969; χ^2 = 7.178; p = 0.007).

RELATING THE PRS-INFORMED EEG COMPONENTS TO RTMS AND CONCURRENT PSYCHOTHERAPY OUTCOME (DATASET 3)

Of the 196 participants, data of 193 were included for translational analysis (sufficient clean EEG and all channels available). No significant correlations between the EEG component and baseline mea-

sures (e.g. age, depression severity, anxiety etc.) were found in men (see Table S2).

First, linear regression analysis of ΔBDI-II on individual EEG component score with age as covariate yielded an R^2 of 5.3% (β = -0.230; p = 0.022) in men, and R^2 of 4.6% (β = -0.215; p = 0.022) when baseline BDI-II score was also added as covariate. The association in women (with age as covariate) was found to be in the other direction, but was not significant (R^2 = 3.4%; β = 0.185; p = 0.068).

Second, to examine categorical outcomes, we performed an ANCOVA with EEG component score as dependent variable and response, sex and rTMS treatment site as fixed factors, and age as covariate yielded a significant ($p<0.05$) response × sex interaction. Repeating the analysis with response as fixed factor for men and women separately resulted in a main effect of response for men (d = 0.576; F = 7.211; p = 0.009), but not women. Adding baseline BDI-II (F = 7.462; p = 0.008) as additional covariate confirmed these results.

A discriminant analysis revealed that age and baseline BDI-II did significantly predict treatment response in men (λ = 0.929; χ^2 = 6.739; p = 0.034), but adding EEG component 4 improved the model (λ = 0.859; χ^2 = 13.914; p = 0.003) with a PPV of 76% and the ROC for this analysis (see figure 4B) yielded an AUC of 0.719 (p = 0.0004; 95%-CI = [0.614-0.824]). A sensitivity analysis with the EEG component alone confirmed significant contribution of the component to rTMS response prediction (λ = 0.930, χ^2 = 6.698, p = 0.010).

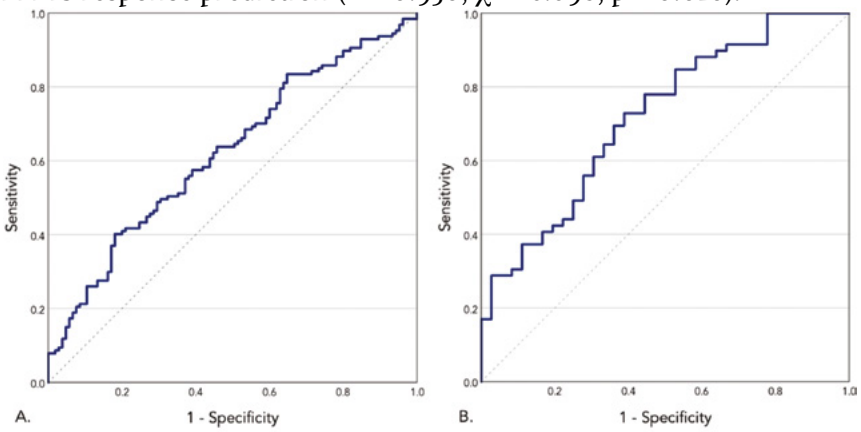


Figure 4. ROC curve of the improved treatment prediction model for response. ROC (receiver operating characteristic) curve for the prediction of medication response (A) and rTMS and concurrent psychotherapy response (B) by the EEG component, age and baseline symptom severity as predictors (improved model), in men.

UTILITY OF THE EEG COMPONENT AS RESPONSE PREDICTOR

The optimal network cut-off point was determined by calculating the maximum Youden index (*J*) of the ROC curves for response of the basic model. The maximum Youden's *J* was at score 1491.055 (*J* = 0.188) for antidepressant medication and 1577.460 (*J* = 0.258) for rTMS (and concurrent psychotherapy) in men, both cut-offs reached a sensitivity of 75%. Response status was predicted based on these cut-off points, which resulted in significantly better within-subsample response rates than expected based on the total observed response rates: PPV = 69% (improvement +26%) and NPV = 52% (p = 0.003) for medication, and PPV = 77% (+24%) and NPV = 48% (p = 0.018) for rTMS (see Table S3 for all results, including sensitivity and specificity).

APPLICATION OF THE EEG COMPONENT AS RESPONSE PREDICTOR (DATASET 4)

Of the 175 patients, 141 were included (receiving CBT or another form of psychotherapy, sufficient clean EEG and all channels available), of whom 50 were male patients with a response rate of 32%. Then, the response status of these male patients was predicted based on the cut-off for rTMS and concurrent psychotherapy. The primary analysis yielded the following results: PPV = 50% (+56%) and NPV = 73% (see Table S4 for all results). A planned sensitivity analysis showed no differences between CBT and other psychotherapies (both PPV = 50%).

DISCUSSION

Given psychological measures mapping poorly on neurobiology and cognizant of the scarce diagnostic and prognostic biomarkers in MDD (Krepel et al. 2019; Van der Vinne et al. 2017; Saveanu et al. 2015), we have here taken a novel, genetics-informed approach to elucidate whether a polygenic-informed EEG signature may help predict differential antidepressant treatment response. This proof-of-concept demonstrates that using a polygenic risk score-informed

data-driven, data-reduction approach applied to resting-state EEG in a large set of hospital-admitted psychiatric patients and healthy controls (dataset 1), we were able to identify one spectral-spatial independent component ('functional network'). We thus uncovered a functional network that in turn was associated with antidepressant medication, as well as rTMS and (concurrent) psychotherapy in independent datasets consisting of MDD patients. This network was found to be a sex-specific, nontreatment-specific, one-directional predictor for antidepressant response in male MDD patients.

Visualizing our functional network (figure 3), we found predominantly slow-wave activity 1) prefrontal jointly left-sided delta power (mainly DLPFC) that was inversely associated with right-sided delta (and theta) power (mainly in the anterior portion of the PFC); 2) slow wave (delta and theta) power in the somatosensory-motor cortex; 3) both slow as well as fast wave power within the visual cortex. This slow-wave network might be difficult to interpret, and does not overlap with prior imaging studies (to our knowledge). Future research should further investigate the exact functional implications of this network and/or validate this against other imaging modalities.

The individual strength of the network was associated with treatment outcome in a sex-specific manner. Several hypotheses might explain the predictive value of the network for antidepressant treatment outcomes in MDD. Abnormalities of the PFC as a network node are known to be implicated in the etiology of MDD and have previously been associated with treatment outcome (Fonseka, MacQueen, and Kennedy 2018). TMS applied to the PFC, however, results in transsynaptic activation of deeper areas such as the subgenual Anterior Cingulate Cortex (Fox et al. 2012) and the frontal-vagal pathway (Iseger et al. 2020). It is plausible that, by modulating neural activity at the stimulation site, TMS synchronically activates remote cortical areas and thereby modulates dysfunctional functional connectivity between areas of the network in a cross-frequency manner. Also, TMS induces anticorrelations between the DLPFC and medial prefrontal areas of the default mode network (Liston et al. 2014).

The predictive value of the network with regards to treatment out-

come was tested in MDD patients prescribed to randomized antidepressant treatment (dataset 2) and treated by rTMS and concurrent psychotherapy (dataset 3). Primary and secondary analyses showed that the network was categorically and dimensionally associated with response to antidepressant medication and rTMS in a sex-specific manner, namely in men only. Two clinical cut-offs (one for psychopharmacotherapy, one for rTMS and concurrent psychotherapy) were established for prediction purposes in male MDD patients. The response rate improved for medication (+26%) as well as rTMS during psychotherapy (+24%) based on these cut-offs. To investigate if the effect was attributed to rTMS or psychotherapy, we blindly and prospectively applied the EEG component and earlier determined clinical cut-off to another independent dataset of MDD patients treated with psychotherapy without rTMS (dataset 4). The response rate improved with 56% in male patients treated with psychotherapy, which could suggest that the former results for rTMS during psychotherapy were driven by psychotherapy.

Unfortunately, based on the results of this study we could not predict treatment outcome in female patients; prediction accuracy measures were restricted to men only. We aimed at performing the latter analysis in two independent datasets consisting of MDD patients treated with rTMS (and sham), but by having to restrict the datasets to male (non)responders, both samples were too small and underpowered, which yielded unreliable and therefore inconclusive results. We suggest replicating this study in larger sample sizes, with a sufficient number of observed responders. Furthermore, the strength of the EEG component lies in predicting the likelihood that the patient is a responder given that the component has identified the patient as a responder. A limitation here, is that the EEG component has no stratification potential, so no alternative treatment strategy – other than the antidepressant treatments studied here – which increases the chance of response, could be determined. Better prediction performance with both high PPV and NPV or/and with stratification potential is desired for clinical purposes. Future research that includes other antidepressant treatments, such as electroconvulsive therapy (ECT), may provide additional insights on predicting beneficial treatment for all MDD patients.

Rest-EEG recordings and subsequent calculation of network score in treatment-naive MDD patients before treatment inception is likely relatively economical and non-invasive. An EEG signature may thus in future provide a useful construct for treatment stratification, thereby enhancing chances of initial response, thus limiting the relative inefficiency of the current stepped-care, 'trial-and-error' approach. Given that efficacy of antidepressant treatment in the general MDD population is moderate (Voigt, Carpenter, and Leuchter 2019; Barth et al. 2016; Simon 2002), and antidepressant discontinuation and switching rates are high (Demyttenaere et al. 2001; Mullins et al. 2005; Goethe et al. 2007), only slightly increased response rates may reduce disease burden and duration.

External validation using two large, independent datasets, and especially the blinded-out-of-sample validation are important strengths of this study. High-density EEG was used for LORETA-fICA, which improves the low spatial resolution compared to low-density EEG, but was only available for the independent datasets used for translational purposes. However, the fICA-LORETA method is applicable to all EEGs independently of apparatus, electrode configuration or number of electrodes since it is derived from the voxel-level rather than the electrode level.

Furthermore, to allow for future clinical translation of our findings we have highlighted several clinically intuitive outcome measures that indicate clinical relevance of the EEG component we retrieve. Nonetheless, limitations of our study include the lack of a placebo-controlled arm, precluding analyses that parse placebo effects. In addition, the network was able to improve the response rates of rTMS with concurrent psychotherapy, but we could not rule out that it was also predictive for rTMS alone. Furthermore, for visualization of neural activity, the fICA-LORETA method calculates power on a categorical scale (i.e. frequency bands) instead of a continuous scale (i.e. power spectrum), thereby limiting the interpretation of the functional networks that are obtained by fICA. Finally, while for our prediction model we relied on the EEG signature, future studies should aim to further optimize prediction by also including other baseline variables, which are likely to further improve the clinical response.

In conclusion, in this proof-of-concept study we show for the first time how a genetics-informed data-driven, data-reduction approach identifies an EEG functional brain network that is of predictive value to MDD treatment. Our method highlights the clinical applicability of such an approach and sets the stage for future stratified psychiatry research.

SUPPLEMENTARY INFORMATION

SUPPLEMENTARY MATERIALS AND METHODS

DNA ISOLATION AND GENOTYPING

DNA was isolated and genotyped for 887 participants admitted to the department of psychiatry at ZNA (Ziekenhuis Netwerk Antwerpen, Belgium) who provided informed consent for DNA extraction and analyses. One 10 ml ethylenediaminetetraacetic acid (EDTA) tube was filled during standard blood draws at the ward. DNA was extracted in the clinical molecular genetics laboratory of the University Medical Center Utrecht (UMCU). Samples were brought to a DNA concentration of 50 ng/µl with a total concentration of 200 ng DNA per participant. Subsequently, samples were sent in two batches to the Human Genotyping Facility of Erasmus Medical Center (Erasmus MC) Rotterdam for Global Screening Array v.1 (GSA) by Illumina, Santa Clara (California), USA, that has excellent validity and reliability (De, Bush, and Moore 2014).

GENETIC QUALITY CONTROL

Quality control (QC) and genetic-ancestry principal component analysis (PCA) were done with PLINK 1.9 (S. Purcell et al. 2007) and performed on the two batches separately (Table S1). Pre-imputation involved the creation of a superset with the highest quality SNPs for subsequent sample QC. The superset of SNPs was created by excluding those with genotype missing call rates >0.01, minor allele frequencies (MAF) <0.1, Hardy-Weinberg equilibrium (HWE) <10-4, and linkage disequilibrium (LD) r^2 >0.2, with a window size of 50 and window shifting of a step size of 5. Using the superset, subjects were removed who: 1) had a mismatch in their sex between reported and genotyped; 2) were too extremely hetero- or homozygous (their F-values differed ≥3 SDs from the mean in the whole cohort); 3) were related (their pi-hat was above 0.1: one of each pair was randomly excluded); and 4) were cohort outliers (had values for the first two ancestry principal components (PCs) that deviated ≥3 SDs from the mean of the whole cohort).

This was followed by a regular SNP-level QC for exclusion of ill performing SNPs: variants with genotyping missing rate >0.01, MAF < 0.01, HWE p-value <10-5 were thus excluded. European ancestry was checked by comparing with the HapMap population: individuals were removed who deviated ≥3 SDs from first and second genetic ancestry PCs from the Northern and Western European (CEU) population.

Lastly, before imputation, genotypic data was compared with the Haplotype Reference Consortium panel. Strands, alleles, positions and frequency differences were checked. Chromosomes were prephased and imputed using the Michigan Imputation Server (Das et al. 2016). Post-imputation QC was performed to include reliable SNPs: variants that had a MAF >0.05 and LD r^2 ≥0.8 were included, resulting in 5,211,700 SNPs available to generate a polygenic risk score (PRS) in 762 individuals remaining after QC.

POLYGENIC RISK SCORE CALCULATION

The summary statistics (Pain et al. 2020) of antidepressant response (AR) were used to generate PRSs (Choi, Mak, and O'Reilly 2020). If only odds ratios (ORs) were reported in the summary statistics, ORs were log-converted to beta values as effect sizes. To that end, the beta values, effective allele, and p-values were extracted from all summary statistics.

SNPs that overlapped between the summary statistics GWASs (training datasets), 1,000 genomes (reference), and our dataset (target) were extracted. Then, insertions or deletions, and ambiguous SNPs, were excluded. To account for complicated LD structure of SNPs in the genome, these SNPs were clumped in two rounds using PLINK 1.90b3z (Chang et al. 2015) according to previously established methods (Schür et al. 2019; McLaughlin et al. 2017); round 1 with the default parameters (physical distance threshold 250 kb and LD threshold (r2) 0.5); round 2 with a physical distance threshold of 5,000 kb and LD threshold (r^2) 0.2. Additionally, we excluded all SNPs in genomic regions with strong or complex LD structures. Sample overlap between training datasets with our target samples is unlikely since all samples belong to different cohorts and no Belgians had been includ-

ed in the aforementioned GWASs used to generate PRSs.
We constructed PRSs based on risk alleles weighted by their effect sizes estimate using PLINK's score function for 11 GWAS p-value thresholds (Purcell et al. 2009; Das et al. 2016): 5×10-6, 5×10-5, 5×10-4, 5×10-3, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1.

EEG RECORDINGS

During EEG recordings, subjects were seated in a sound and light attenuated room that was controlled at an ambient temperature of around 22°C. The participants were instructed to sit still for the duration of the recording without thought instructions. The operator did not intervene when drowsiness patterns were observed in the EEG.
Resting-state eyes closed EEG recordings for dataset 1 were acquired from 65 channels of the Electrical Geodesics Incorporated (EGI; Magstim, UK) system (dataset 1) and from 26 channels (10-20 electrode international system: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, and O2) of the Neuroscan NuAmps (Compumedics, Australia; dataset 2 and 3). Data were recorded for three (dataset 1) or two (dataset 2 and 3) minutes during eyes closed condition. The sampling frequency was 500 Hz for most recordings, but 1,000 Hz for 6 recordings in dataset 1 (which were down-sampled to 500 Hz prior to further analyses). Data were referenced to Cz (dataset 1) or average mastoids with a ground at AFz (dataset 2 and 3). Horizontal eye movements were recorded with electrodes 61 and 64 (dataset 1) or electrodes placed 1.5 cm lateral to the outer canthus of each eye (dataset 2 and 3). Vertical eye movements were recorded with electrodes 5 and 62 (dataset 1) or electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid (dataset 2 and 3). Cartesian coordinates of the EGI system electrodes (dataset 1) were converted to spherical coordinates prior to EEG preprocessing.

LORETA-FICA MODEL

The typical ICA model assumes that the source signals are not observable, statistically independent and non-Gaussian, with an un-

known, but linear, mixing process (Calhoun, Liu, and Adali 2009), and is described by the following formula:

$x = As$

where x, A and s represent matrices. In our case, these three matrices consisted of the following data:

1. Matrix x with 1,123 rows corresponding to all subjects of dataset 1, and the data per subject consists of 37,434 (6,239x6) columns corresponding to the spectral power at 6,239 cortical voxels for the six frequency bands. This approach, using a priori determined frequency bands, is a unique feature of the method used (Pascual-Marqui and Biscay-Lirio 2011).
2. Matrix s with 29 rows corresponding to the number of statistically independent components (i.e. functional networks), and 37,434 columns. In this way, each functional network contains 6 spatial images corresponding to neural activity of each frequency band (i.e. in a cross-frequency manner).
3. Matrix A with 1,123 rows and 29 columns. Thus, what remains of this data reduction for every subject is the amount of each component that was used for that subject. This amount is expressed as a loading (i.e. signed weight or score) per functional network for each subject.

SUPPLEMENTARY RESULTS

Quality control steps[a]	*Subjects*		*SNPs*	
	Batch 1	Batch 2	Batch 1	Batch 2
Data available for QC genotyping	537	350	686,082	692,319
Pre-imputation steps (separate batches)				
Individuals >0.05 missing genotypes	-4	-0		
Creating SNP superset	533	350	686,082	692,319
Genotype rate <0.01, MAF <0.1, HWE $<1\times10^{-4}$, LD pruning (50 5 0.2)			-545,698	-530,759
Perform subject-level QC with SNP superset	533	350	140,384	161,560
Sex check, heterozygosity (≥3 SD), relatedness, (≥3 SD) pi-hat >0.1, genetic outliers	-20	-62		
Normal SNP QC	513	288	686,082	692,319
Genotype rate <0.01, MAF <0.01, HWE $<1\times10^{-5}$			-227,781	-197,418
Compare with HapMap	513	288	458,301	494,901
Removal of genetic outliers (≥3 SD) from HapMap-CEU	-1	-18		
Retained after pre-imputation QC	512	270	458,301	494,901
Post-imputation steps (merged batches)				
Imputed total			16,271,699	
QC (MAF <0.05, LD R2 ≥0.8)			-11,059,999	
FINAL post-imputation TOTAL	762[b]		5,211,700	

Table S1. QC steps of genotype data. *Abbreviations: QC = quality control; SD = standard deviation; SNP = single nucleotide polymorphism; MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium; LD = linkage disequilibrium; PC = principal component; HapMap = haplotype map; GSA = global screening array.*
[a] '-' is referring to excluded in this QC step; [b] 762 individuals retained after post-imputation QC, of those 40 were excluded after EEG preprocessing.

Baseline characteristic	Effect size of Pearson correlation with independent EEG component 4			
	Pharmacotherapy		*Transcranial magnetic stimulation (TMS)*	
	Women	Men	Women	Men
Age	r = 0.010 (p > 0.05)	r = 0.015 (p > 0.05)	r = -0.082 (p > 0.05)	r = 0.013 (p > 0.05)
Years of education	r = -0.122 (p = 0.038)	r = 0.078 (p > 0.05)	r = -0.023 (p > 0.05)	r = -0.174 (p > 0.05)
BDI-II/QIDS	r = 0.110 (p > 0.05)	r = -0.028 (p > 0.05)	r = 0.218 (p = 0.031)	r = -0.045 (p > 0.05)
DASS-anxiety	r = -0.030 (p > 0.05)	r = 0.066 (p > 0.05)	r = 0.028 (p > 0.05)	r = 0.036 (p > 0.05)
DASS-stress	N/A N/A	r = 0.008 (p > 0.05)	r = -0.017 (p > 0.05)	
DASS-depression	N/A N/A	r = 0.296 (p = 0.004)	r = -0.067 (p > 0.05)	

Table S2. Correlation between the LORETA-fICA component and baseline characteristics. *Abbreviations: QIDS = Quick Inventory of Depressive Symptomatology; BDI-II = Beck Depression Inventory, second edition; DASS = Depression Anxiety Stress Scales; N/A = data for analysis not available.*

ADDITIONAL INFORMATION:

Pearson correlation analyses showed significant correlations at $p<0.05$ between the obtained LORETA-ICA EEG component with baseline depression symptom severity in the rTMS sample and with educational level in the iSPOT-D sample (see Table S2) in women, but not in men.

	Antidepressant medication[a]		*rTMS and concurrent PT*[b]	
	obs. R	obs. NR	obs. R	obs. NR
R-pred.	**N = 53**	**N = 24**	**N = 30**	**N = 9**
NR-pred.	N = 74	N = 81	N = 29	N = 27
total	N = 127	N = 105	N = 59	N = 36
prediction performance				
	PPV	NPV	PPV	NPV
	69%	52%	77%	48%
	Sensitivity	Specificity	Sensitivity	Specificity
	42%	77%	51%	75%
statistics	Fisher	V	Fisher	V
	0.003*	0.2	0.018*	0.255

Table S3. Response prediction based on network loading cut-offs male MDD patients.
Abbreviations: rTMS = repetitive transcranial magnetic stimulation; PT = psychotherapy; R = response; NR. = non-response; obs. = observed (numbers of true responders and non-responders in the dataset); pred. = predicted (based on two cut-offs); PPV = positive predictive value; NPV = negative predictive value; Fisher = Fisher exact test; V = Cramérs V (effect size).
*[a] cut-off point = 1,491; [b] cut-off point = 1,577; * exact two-tailed p-value from Fisher's test.*

	Psychotherapy	
	obs. R	obs. NR
R-pred.	N = 5	N = 5
NR-pred.	N = 11	N = 29
total	N = 16	N = 34
prediction performance		
	PPV	NPV
	50%	73%
	Sensitivity	Specificity
	31%	85%

Table S4. Blinded out-of-sample validation of the EEG signature in male MDD patients.
Abbreviations: R = response; NR = non-response; obs. = observed (numbers of true responders and non-responders in the dataset); pred. = predicted (based on cut-off); PPV = positive predictive value; NPV = negative predictive value.

3

A POSTERIOR-ALPHA AGEING NETWORK IS DIFFERENTIALLY ASSOCIATED WITH ANTIDEPRESSANT EFFECTS OF VENLAFAXINE AND RTMS

ABSTRACT

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder, but chances for remission largely decrease with each failed treatment attempt. It is therefore desirable to assign a given patient to the most promising individual treatment option as early as possible. We used a polygenic score (PGS)-informed electroencephalography (EEG) data-driven approach to identify potential predictors for MDD treatment outcome. Post-hoc we conducted exploratory analyses in order to understand the results in depth. First, an EEG independent component analysis produced 54 functional brain networks in a large heterogeneous cohort of psychiatric patients (N = 4,045; 5-84 yrs.). Next, the network that was associated to PGS for antidepressant-response (PRS-AR) in an independent sample (N = 722) was selected: an age-related posterior alpha network that explained >60% of EEG variance, and was highly stable over recording time. Translational analyses were performed in two other independent datasets to examine if the network was predictive of psychopharmacotherapy (N = 535) and/or repetitive transcranial magnetic stimulation (rTMS) and concomitant psychotherapy (PT; N = 186) outcome. The network predicted remission to venlafaxine ($p = 0.015$), resulting in a normalized positive predicted

value (nPPV) of 138%, and rTMS + PT – but in opposite direction for women ($p = 0.002$) relative to men ($p = 0.018$) – yielding a nPPV of 131%. Blinded out-of-sample validations for venlafaxine ($N = 29$) and rTMS + PT ($N = 36$) confirmed the findings for venlafaxine, while results for rTMS + PT could not be replicated. These data suggest the existence of a relatively stable EEG posterior alpha ageing network related to PGS-AR that has potential as MDD treatment predictor.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders, affecting over 300 million people worldwide and leading to over 50 million years lived with disability. Prevalence rates vary by age, peaking in older adulthood and are higher for women than men at all ages (WHO 2017). Pharmacotherapy and psychotherapy constitute effective (first-line) treatment options, but the majority of patients do not achieve remission after their first treatment attempt. These patients therefore require several treatment steps, with one third still not sufficiently responding (failing to remit) after four sequential treatment steps (Rush et al. 2006). When patients don't respond to medication and/or psychotherapy, the clinician may also consider repetitive transcranial magnetic stimulation (rTMS), a non-invasive, well-tolerated brain stimulation method efficacious in the treatment of MDD (Lam et al. 2008).

Despite these various effective treatment options for patients with MDD, little is known about the underlying biological or clinical prognostic factors that could predict treatment outcome, leading to an undesirable trial-and-error approach in treatment selection for a given patient. Recent evidence suggests that antidepressant treatment response has a complex polygenic architecture (Pain et al. 2020), which warrants studying polygenic scores (PGS) (Lewis and Vassos 2020), instead of individual variants that predict antidepressant response (Nøhr et al. 2022). Regarding biological factors, antidepressant efficacy differs between the sexes, and various possible underlying mechanisms have been proposed, including differences in synaptic

transmission and pharmacokinetics (LeGates, Kvarta, and Thompson 2019). We previously demonstrated sex-specific differences in biomarkers related to antidepressant response for alpha-asymmetry (Arns et al. 2016), connectivity (Iseger et al. 2017), and event-related potentials (Dinteren et al. 2015). Therefore, it may be advantageous for biomarker research on depression to focus on female and male patients separately.

Electroencephalography (EEG) oscillations, generally described in terms of frequency bands, could provide such biomarkers for psychiatric disorders (Silva 2013). A wide range of potentially useful features can be derived from the EEG, such as band power and network-based metrics, and some have been previously associated with antidepressant outcome: decreased parieto-occipital alpha power for example predicts poor antidepressant response (Olbrich and Arns 2013). Functional brain network measures have been found to be heritable, to change with normal aging, and to be abnormal in clinical disorders (Bassett and Bullmore 2009), and are thus of interest for biomarker research. Functional independent component analysis (fICA) using eLORETA (exact Low Resolution Brain Electromagnetic Tomography) is a method for extracting information from the EEG by separating multivariate EEG signals into additive independent spectral-spatial components, or functional brain networks (Aoki et al. 2015).

Given the low chances of remission following each antidepressant treatment on the one hand and the lack of firmly established biomarkers for such treatments on the other, there is interest in biomarkers to help guide individualized treatment and thereby reduce chances of unsuccesful treatment trials. In a recent proof-of-principle study, combining PGS for antidepressant response (PGS-AR) with eLORETA-fICA, we demonstrated how a polygenic-informed EEG data-driven, data-reduction approach within a large dataset of more than thousand adult psychiatric patients, resulted in an EEG signature that was associated with MDD treatment response, in male patients only (Meijs et al. 2022). In the current follow-up study, we aimed to identify a functional brain network capable of differentially predicting remission to MDD treatments in men and women. The eLORETA-fICA was applied to a lifespan database consisting of more

than 4,000 psychiatric patients, to better capture functional brain networks across the lifespan. Subsequently, an association analysis with PGS-AR was performed in an independent dataset to select a functional network with expected prognostic potential. In four independent datasets, translational and subsequent blinded-out-of-sample approaches were conducted to test the predictive value of the network.

MATERIALS AND METHODS

Our approach is visualized in figure 1.

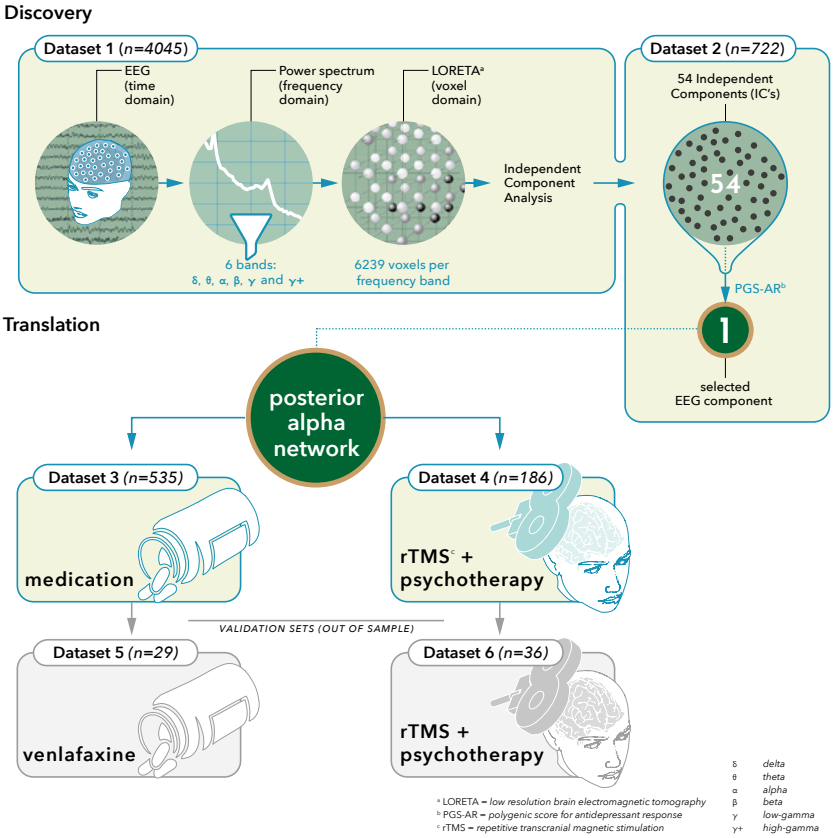


Figure 1. *Flowchart depicting the study set-up and analysis pipeline. The first part of the discovery analysis (dataset 1: TDBRAIN+), using the eLORETA-fICA method, is shown upper left. Data for this method consisted of six a priori defined frequency bands and 6239 voxels (6x6239) per subject. This resulted in 54 independent cross-frequency spectral-spatial components. In the second part of the discovery analysis (dataset 2) we found the first fICA component (EEG component 1; an alpha posterior network) to be robustly associated with the polygenic score for antidepressant response (PGS-AR) in men and women, shown upper right. This alpha posterior network was used for translational purposes in two independent datasets: depressive patients treated with pharmacotherapy (dataset 3; iSPOT-D) or rTMS and concomitant psychotherapy (rTMS + PT; dataset 4), which is shown below. Network activity of the posterior alpha network was associated with remission and response to both venlafaxine and rTMS + PT. In another independent dataset (dataset 5), consisting of patients who received venlafaxine, results were validated. The findings for rTMS + PT could not be replicated (dataset 6).*

DATASET 1: PARTICIPANTS FOR THE FICA IN ELORETA

The Two Decades-Brainclinics Research Archive for Insights in Neurophysiology (TDBRAIN), in addition to data from other clinics (TDBRAIN+) was used for the first analysis (also see Voetterl et al., 2022 (Voetterl et al. 2022)). TDBRAIN+ contains clinical lifespan (5-89 years) resting-state eyes-closed EEG data complemented with relevant clinical and demographic data of a heterogeneous collection of patients and healthy participants. The open access TDBRAIN dataset is freely available at http://www.brainclinics.com/resources, with all data recorded at Research Institute Brainclinics (Brainclinics Foundation, Nijmegen, The Netherlands (Van Dijk et al. 2022)). TDBRAIN+ was used for fICA and consisted of 4,045 participants (clean preprocessed EEG data suitable for fICA). All participants (or their guardians when underaged) provided written informed consent.

DATASET 2: PARTICIPANTS FOR THE PGS-INFORMED EEG COMPONENT SELECTION.

The second dataset was a sample from Meijs et al. (Meijs et al. 2022) and consisted of 722 adult participants (clean preprocessed resting-state eyes-closed EEG data as well as genome-wide data that had undergone extensive individual and genotype-level quality control, QC) with a variety of psychiatric diagnoses. The study was approved by the Institutional Review Board of Ziekenhuis Netwerk Antwerpen. All participants provided written informed consent. Further details, such as genotype-level QC and the calculation of polygenic scores have been published by Meijs et al. (Meijs et al. 2022).

DATASET 3: PARTICIPANTS FOR TRANSLATION ANALYSIS (ISPOT-D ANTIDEPRESSANT MEDICATION).

The third dataset was the iSPOT-D sample (International Study to Predict Optimized Treatment in Depression), an international multicenter, randomized, prospective open-label trial (phase-IV clinical trial). This study consisted of 1,008 patients diagnosed with non-psychotic MDD who were randomized to one of the selective serotonin reuptake inhibitors (SSRIs) escitalopram or sertraline, or to the sero-

tonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine. The study protocol was approved by the institutional review boards at all of the participating sites and this trial was registered with ClinicalTrials.gov under id NCT00693849. All participants provided written informed consent. At baseline and after eight weeks of treatment patients filled in the Quick Inventory of Depressive Symptomatology (QIDS). Only data from participants who completed eight weeks of randomized medication treatment ('per protocol' sample) were included. Details about this sample have been published elsewhere (Arns et al. 2016; Williams et al. 2011).

DATASET 4: PARTICIPANTS FOR THE TRANSLATIONAL APPROACH (RTMS AND CONCURRENT PSYCHOTHERAPY)

The fourth dataset consisted of 196 patients diagnosed with non-psychotic MDD, who were treated with high-frequency TMS (10-Hz left dorsolateral prefrontal cortex, DLPFC) or low-frequency TMS (1-Hz right DLPFC); a minority received both 1-Hz and 10-Hz sequentially. All patients completed at least ten sessions of treatment, and filled in the BDI-II at baseline and at the last session (on average session 21). Concurrent with rTMS, patients received psychotherapy (rTMS + PT). All participants provided written informed consent. Details about this sample are described elsewhere (Donse et al. 2017; Krepel et al. 2019).

DATASET 5: PARTICIPANTS FOR BLINDED OUT-OF-SAMPLE VALIDATION (VENLAFAXINE).

The fifth dataset included patients diagnosed with non-psychotic MDD or dysthymia and a BDI-II score ≥14 at baseline, who received venlafaxine, either as monotherapy (N = 9) or in combination with psychotherapy (N = 20). Response and remission were based on the BDI-II score at intake (baseline), and again after eight weeks of medication (monotherapy) or at the end of psychotherapy if this preceded the eight weeks of medication (combination). For more details, see Van der Vinne et al. (Van der Vinne et al. 2021)

DATASET 6: PARTICIPANTS FOR BLINDED OUT-OF-SAMPLE VALIDATION (1-HZ RTMS).

Data for the sixth dataset were collected in the same way as dataset 4 described in Voetterl et al. (Voetterl 2023). In short, 36 patients diagnosed with non-psychotic MDD or dysthymia and BDI-II ≥14 at baseline, received protocolized 1-Hz rTMS + PT. Response and remission were based on the BDI-II score at baseline and after treatment completion, at least ten treatment sessions.

EEG RECORDINGS AND PREPROCESSING

Resting-state eyes closed EEG recordings (for more details see Supplementary Methods and Materials) for all datasets were acquired using a 26-channel system of the Neuroscan NuAmps, Quickcap or ANT-Neuro Waveguard Cap (Compumedics, Australia) except for dataset 2, here we used the 65-channel cap (64-channel plus Cz) of the Electrical Geodesics Incorporated (EGI; Magstim, UK) system.
For TDBRAIN+ (dataset 1), previously published automatic preprocessing routines were adapted to be compatible for use in Python described by Van Dijk et al. (Van Dijk et al. 2022), while Brain Vision Analyzer 2.0 (Brain Products, Germany) software was used for subsequent digital signal-processing in the other datasets.

In short, the following steps were taken in the EEG preprocessing: data were bandpass-filtered, the notch-frequency was removed; electro-oculography (EOG) was corrected using a regression-based technique (Gratton, Coles, and Donchin 1983), while noisy signals or flat lines were corrected by spherical spline interpolation. Artifacts were removed in Brain Vision Analyzer by rejection of epochs that did not meet the criteria (maximal allowed difference of 150 μV peak-to-peak), or using the preprocessing pipeline (Python (Van Dijk et al. 2022), and also available at www.brainclinics.com/resources): signals that contained artifacts for more than 66% of the measurement were repaired using a Euclidian distance weighted average of at least three neighboring channels. All data were segmented into epochs of four seconds.

eLORETA-FICA model

The EEG was used for estimating the cortical source distribution of electric neuronal activity by means of eLORETA (exact low-resolution electromagnetic tomography; free academic software available at https://www.uzh.ch/keyinst/loreta). This method weights minimum norm inverse solution, and localization inference is based on the standardized estimates of the current density (Pascual-Marqui et al. 2011).

In short, the following analysis steps, as described in our prior proof-of-principle study (Meijs et al. 2022) were performed. First, each EEG recording (epoch) was transformed to the frequency domain. Cross-spectral matrices were obtained for six predefined frequency bands: delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), beta (14.5-30 Hz), low-gamma (31-47 Hz), and high-gamma (>70 Hz). Second, from each cross-spectrum matrix, the spectral density was computed for each cortical voxel. Third, the spectral-spatial data of all subjects were concatenated as input for the independent component analysis (ICA), aiming to identify cross-frequency, independent spectral-spatial components (i.e. functional networks). This method was recently validated in our proof-of-principle study (Meijs et al. 2022) as well as in Aoki et al. (Aoki et al. 2015) and Gerrits et al. (Gerrits et al. 2019), where it reliably identified DMN (default mode network) and TP (task-positive) networks.

Independent components

Each functional network (fICA component) represents sets of brain regions that are consistently activated or deactivated together within and across given frequency band(s). An optimal number of components was determined using the Bayesian Information Criterion (BIC). To visualize the functional networks (i.e. (anti)correlated brain regions), a threshold was set at three z-values. Per fICA component, scores were obtained for each participant, corresponding to the activity of the network for a given individual subject. The functional networks that were established based on the first dataset, were prospectively applied to the other datasets. Likewise, for each subject in each dataset, EEG component scores were obtained per network. These scores were used in the statistical analyses.

OUTCOME MEASURES

For component selection (dataset 2), the independent EEG components were regressed on PGS-AR. In line with prior work (Voetterl et al. 2022), we primarily focused on remission as an outcome measure, and secondarily on response. Outcomes were based on the Quick Inventory of Depressive Symptomatology (QIDS) for the iSPOT-D sample (dataset 3) and Beck Depression Inventory II (BDI-II) for the rTMS + PT sample (dataset 4), which are both self-report questionnaires, taken at intake and after treatment completion (on average at week eight for antidepressants and at session 21 for rTMS). Remission was defined as a score of ≤5 on the QIDS or ≤12 on the BDI-II, and response was defined as ≥50% reduction relative to the baseline score, both at treatment completion.

STATISTICAL ANALYSES

SPSS (IBM SPSS Statistics for Macintosh (Version 27.0) 2020) was used for statistical analyses. Effect sizes (ES) of significant main effects are reported as Cohen's d (*d*) for binary measures or as explained variance (R^2) and/or standardized beta (β) for continuous measures. Two-sided tests were performed for statistical significance testing.
To examine potential sex-specific associations, sex was included as main factor, or – in case the analysis could not accommodate sex as main factor – women and men were analysed separately, rather than handled as covariate since covariation can only resolve quantitative (not qualitative) sex differences. If no sex interaction with outcome was found, or the effect for both sexes was in the same direction, analyses were performed on men and women combined. We then applied a series of analyses to discover an EEG component with predictive value on outcome.

First, after generating the EEG component scores (as described above) in dataset 1, for our discovery analysis we examined if there was an association between these fICA components and PGS-AR (dataset 2). To that end, linear regression, controlling for age and the first five genetic ancestry principal components (PCs), was run between all individual component scores and 11 PGS-ARs binned at p-value thresholds (P_T = 5.0×10^{-6} to P_T = 1) to choose the optimal P_T, which is unknown a priori (Choi, Mak, and O'Reilly 2020). The significance level was correct-

ed for the number of components and sex-specific subgroup analyses and therefore set to $\alpha = 0.05/(54\times3) = 0.0003$. The EEG component (i.e. functional network) that showed the most significant association with PGS-AR was selected for subsequent analyses.

Second, translational analyses were performed (dataset 3 and 4) to examine if the selected network was associated with psychopharmacotherapy and/or rTMS + PT remission. The significance level for these follow-up analyses was set at conventional $\alpha = 0.05$ as these analyses were intended for translation of the findings in the discovery analysis. Subsequent blinded-out-of-sample validation datasets were available to verify obtained any associations detected. Factorial ANCOVAs were run to establish whether the individual network scores were significantly different in remitters compared to nonremitters. Sex was added as fixed factor to analyse sex interactions; for medication SSRI versus SNRI and for rTMS 10-Hz versus 1-Hz were also added as fixed factors to analyse treatment arm effects. Age and baseline severity scores were added as covariates to these models.

If the ANCOVA showed significant main effects, a discriminant analysis was performed to assess the predictive value of the selected functional network as a single predictor. Mediation analyses by PROCESS version 4.0 for SPSS (Hayes 2020) were done to investigate if age or baseline severity mediated the relationship between the network and remission, covarying for baseline severity or age. The optimal network score cut-off points for classifying patients as 'remitter' of 'nonremitter' were determined by calculating the maximum Youden Index (*J*), which measures the accuracy of a dichotomous diagnostic test. Based on these cut-offs, a prediction model was built to evaluate the clinical utility of the network for prediction purposes, by calculating the positive predictive value (PPV), normalized PPV (nPPV; corrected for the actual remission rate) and overall predictive value (equal to accuracy) in a crosstabulation.

Finally, to better understand the selected functional network in terms of transdiagnostic aspects, we conducted explorative post-hoc analyses and looked at various transdiagnostic factors such as age, personality, sleep, depression and anxiety scores and cognitive performance.

To that end, Spearman correlation analyses were run within the TD-BRAIN+ sample between network score and 12 different transdiagnostic clinical and demographic variables: age, hours of sleep the night before the EEG acquisition, scores on the 'big five' personality dimensions, scores on the three Depression Anxiety Stress Scale (DASS) subscales, and false positive and negative scores on the auditory oddball test (for a description see Supplementary Methods and Materials). The significance level was Bonferroni-corrected for the number of variables, as well as the number of sex-specific (male vs. female) and age-specific (adult vs. non-adult) subgroup analyses, resulting in $\alpha = 0.05/(12\times4) = 0.001$, and effect sizes of $\rho>0.1$ were considered relevant. We also examined fICA scores across time over 10 artifact-free 4-second epochs to assess stability of the obtained network (i.e. test-retest reliability) and to what degree the network exhibits vigilance or arousal-related changes over time (Arns et al. 2011; Olbrich et al. 2016), and thus served as a proxy for vigilance stages. Prior research under resting conditions hints at hyperstable vigilance regulation in depression (Hegerl et al. 2011). To that end, every first available 4-second epoch, starting within ten consecutive timeframes of 10 seconds, was selected for each subject. Consequently, a maximum of ten epochs (since there were ten timeframes) per subject were available for the analyses. The intraclass correlation coefficient (ICC) was computed, based on an absolute agreement, two-way mixed-effects model (Hallgren 2012), to assess test-retest reliability. A one-way repeated measures ANOVA was performed with time (ten levels) as repeated-measures variable, and age-group (five groups in years: 5-11; 12-17; 18-29; 30-49; 50+) and sex as between-subjects factor. Lastly, the network score slope over all epochs as well as differences between the first and last epoch were calculated for correlation analyses with baseline variables.

RESULTS

An overview of the baseline demographic characteristics and response and remission rates per dataset after EEG preprocessing can be found in Table 1. In brief, we included 5,553 participants in total from six independent datasets for the analyses. Dataset 1 and dataset 2 included psy-

chiatric patients and a relatively small number of healthy participants, while the other datasets included MDD patients only.

Baseline characteristics	*Dataset 1: Discovery (fICA)*	*Dataset 2: Selection (PGS-AR)*	*Dataset 3: Translation 1 (AD)*	*Dataset 4: Translation 2 (rTMS + PT)*	*Dataset 5: Validation 1 (AD and/or PT)*	*Dataset 6: Validation 2 (rTMS + PT)*
Total number of participants	4249	1195	1008	196	195	36
N included in study	4045[1]	722[2]	535	186	29[3]	36
Women	40%	47%	54%	50%	88%	56%
Mean age (SD), years	28.7 (18.3)	41.9 (13.8)	38.5 (12.6)	43.3 (12.9)	42.5 (15.1)	44.4 (16.2)
Self-report; mean baseline score (SD)	N/A	BDI-II; 26.5 (14.8)	QIDS; 14.5 (3.7)	BDI-II; 30.8 (9.8)	N/A[4]	N/A[4]
Remission rate	N/A	N/A	36%	55%	21%	47%
Response rate	N/A	N/A	52%	66%	28%	61%

Table 1. Baseline characteristics. *Abbreviations: fICA = functional independent component analysis; PGS-AR = polygenic score for antidepressant response; AD = antidepressant medication; rTMS = repetitive transcranial magnetic stimulation; PT = psychotherapy; BDI-II = Beck Inventory Index, second version; QIDS = Quick Inventory of Depressive Symptomatology; SD = standard deviation.*

[1] This dataset was used for functional independent component analysis (fICA), but demographics and clinical data were available for N = 3914 (sex data) and N = 3845 (age data).

[2] This is a subset of the total of 1195 participants, for whom preprocessed EEG data and genetic data after quality control were available.

[3] Number of patients treated with venlafaxine (with/without concurrent PT).

[4] N/A as this was a blinded out-of-sample validation; hence self-report scores were unknown at the time of analysis, and actual remission/response rates and (normalized) positive predictive values rates were confirmed by an independent third person.

DISCOVERY ANALYSIS IDENTIFIES 54 COMPONENTS USING ELORETA-FICA

The sample for eLORETA-fICA consisted of 4,045 participants. The BIC was used for estimating the number of significant components, which indicated 54; hence the fICA was constrained to 54 components that explained 98.6% of the total signal variance (see figure 1: discovery).

POLYGENIC-INFORMED SELECTION OF THE POSTERIOR ALPHA NETWORK

The sample for PGS association analysis consisted of 722 participants (remaining after EEG preprocessing and genetic QC). An association was found between PGS-AR and EEG component 1, and no other

components. This component explained 60.8% of the total EEG variance The strongest and most significant association between this component and PGS-AR was at $P_T<5\times10^{-3}$ in both male and female participants ($\beta = -0.137$; $R^2 = 1.90\%$; $p = 0.000265$; figure S1). We therefore used this component for validation analyses.

Figure 2 shows EEG component 1, representing joint deactivation and activation of neural activity (only within the alpha frequency band) coming from sets of posterior regions that form functional spatial-spectral networks. EEG alpha power changes in the parietal lobe were inversely correlated with alpha power changes in the occipital lobe (visual cortex). A high component score was associated with more parietal alpha activity, while a low score was associated with predominantly occipital alpha activity. We will refer to this component as the 'posterior alpha network'. The individual scores of this network positively correlated with age at baseline in all datasets, except in dataset 2 used for PGS analysis (no correlation), but not with baseline severity (BDI-II or QIDS; figure 2).

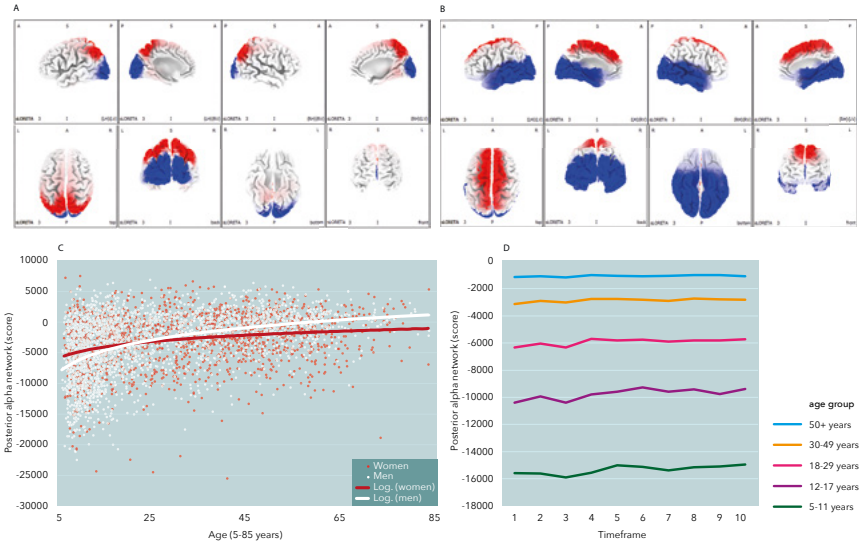


Figure 2. *Functional network of the component obtained with eLORETA-fICA. The upper map visualizes the posterior alpha network (EEG component 1), using eLORETA-fICA, viewed from eight different angles (anterior [A], posterior [P], superior [S], inferior [I], left [L], right [R], left view [LV], right view [RV], left hemisphere [LH] and right hemisphere [RH]). The component covers alpha activity in different brain regions (A). The two colors represent joint neural activation and deactivation: EEG alpha power changes in the parietal lobe (red; Brodmann area [BA] 7, 19, 39 and 40) were inversely correlated with EEG alpha power changes in the occipital lobe (blue; BA 17, 18 and 19). This contrast becomes clearer when the differences (at p<0.01) between the 1000 highest (red) and 1000 lowest (blue) network scores are visualized as in the top-right map (B). Thus, a relatively high network score was related to predominantly midline (frontal and parietal) neuronal activity and a relatively low score to predominantly posterior (occipital) activity. The charts below depict the relation between the posterior alpha network and age as well as time. There was a positive correlation between age and the network score (the older, the higher the network score). This correlation was stronger in male participants. Also, the variance of the network score was largest in children (the younger, the larger the variance), with the lowest network scores more often seen in children (C). There was a small effect of age group on network score changes over 10 seconds timeframes, and a large effect was found between age groups (D).*

TRANSLATIONAL ANALYSES IN TWO INDEPENDENT TREATMENT RESPONSE DATASETS

The primary outcome for translational analysis (see figure 1: translation) was categorical remission, the secondary outcome was response.

RELATING THE POSTERIOR ALPHA NETWORK TO ANTIDEPRESSANT MEDICATION OUTCOME

Of the 1,008 (dataset 3) participants, data of 535 were included for translational analysis (treated per protocol, sufficient clean EEG and all channels available).

First, to examine categorical outcomes, we performed a factorial ANCOVA with network score as dependent variable. This yielded a significant ($p = 0.042$) remission × type of antidepressant interaction. Repeating the analysis with remission as fixed factor for SSRIs (escitalopram or sertraline) and SNRIs (venlafaxine) separately resulted in a main effect of remission for venlafaxine ($d = 0.410$, $F = 5.30$, $p = 0.023$), but not for escitalopram or sertraline.

Second, a discriminatory analysis was performed: the alpha posterior network alone significantly predicted remission with venlafaxine (Wilk's Lambda, $\lambda = 0.964$; Chi-Square, $\chi^2 = 5.933$; $p = 0.015$). The area under the curve (AUC) of remission for alpha posterior network (AUC = 0.623) slightly improved when successively age (AUC = 0.628) and baseline QIDS (AUC = 0.664) were added to the predictive model (see figure S2A). Response data demonstrated similar results overall (see Supplementary Results). There were no mediation effects of age or baseline severity.

Subsequently, the optimal network score cut-off point within the venlafaxine group was determined by calculating the maximum Youden index for remission, which was $J = 0.268$ (sensitivity = 63.2%). Classifying patients as 'remitter' or 'nonremitter' based on this cut-off, resulted in a PPV of 48% (nPPV = 138%) and overall predictive value of 63.4% (Cramer's $V = 0.255$; $p = 0.002$) for venlafaxine (see Table S1A). Stratification of the full sample (i.e. assigning patients treated with an SSRI in the opposite direction than venlafaxine users, but based on the cut-off

for venlafaxine) resulted in a PPV of 40.9% (nPPV = 112%). The PPV within the SSRI group was 37.7% (nPPV = 101%).

RELATING THE POSTERIOR ALPHA NETWORK TO RTMS AND CONCURRENT PSYCHOTHERAPY OUTCOME

Of the 196 (dataset 4) participants, data of 186 were included for translational analysis (treatment protocol 10-Hz or 1-Hz and not sequentially, sufficient clean EEG and all channels available).

First, to examine categorical outcomes, we performed a factorial ANCOVA with network score as dependent variable. This yielded a significant ($p < 0.001$) remission × sex interaction but no protocol interaction. Repeating the analysis with remission as fixed factor for men and women separately resulted in a main effect of remission for men ($d = 0.495$, $F = 12.48$, $p < 0.001$), and women ($d = -0.682$, $F = 16.07$, $p < 0.001$).

Second, a discriminant analysis was performed and revealed that the alpha posterior network as single predictor significantly predicted remission ($\lambda = 0.899$, $\chi^2 = 9.650$, $p = 0.002$) in women. For men the predictive value was in the opposite direction for remission ($\lambda = 0.940$, $\chi^2 = 5.626$, $p = 0.018$). The AUC of remission for the alpha posterior network (women: AUC = 0.657; men: AUC = 0.638) improved when successively age (AUC = 0.716; AUC = 0.711) and baseline BDI-II (AUC = 0.855; AUC = 0.762) were added to the predictive model (see figure S2B and S2C). Again, response data overall demonstrated similar results (see Supplementary Results).

A mediation analysis showed that age was a significant mediator of the relation between network score and rTMS + PT remission and response in men, while this was not found in women. An ANOVA yielded no significant age differences between remitters and nonremitters in both sexes, but a significant age difference between responders and nonresponders to rTMS + PT in men only ($p = 0.019$): male responders were younger. We found no mediation effects of baseline BDI-II score on either remission or response in both women and men.

The optimal network score cut-off points for remission were determined, which was $J = 0.321$ (sensitivity = 92.9%) in women and $J = 0.300$ (sensitivity = 78.8%) in men. Classifying patients based on these cut-offs resulted in a PPV of 72.6% (nPPV = 131%) and overall predictive value of 65.1% (Cramer's V = 0.307; $p < 0.001$) for rTMS + PT (see Table S1B). As sensitivity analysis, the same analysis was performed for both rTMS protocols separately, resulting in a PPV of 76.5% (nPPV = 130%) for 10-Hz and PPV of 70% (nPPV = 132%) for 1-Hz.

Lastly, to investigate if the predictive value of the posterior alpha network was driven by rTMS treatment, psychotherapy or both, ANCOVA and discriminant analyses were repeated in an independent sample of MDD patients treated with psychotherapy (N = 137), but not with rTMS or medication. No significant effect nor trend towards significant results were found; we thus assume effects were not driven by psychotherapy alone.

BLINDED OUT-OF-SAMPLE VALIDATION OF THE POSTERIOR ALPHA NETWORK

We performed two blinded (treatment outcome not known by classifying researcher) out-of-sample validations based on the cut-off point for venlafaxine and rTMS + PT in two independent datasets to validate and replicate the previous findings.

VENLAFAXINE

In the first independent out-of-sample dataset of 29 MDD patients treated with venlafaxine with an overall remission rate of 21% (dataset 5), blinded classification (remission vs. nonremission) based on the posterior alpha network score, resulted in a PPV of 33% (nPPV = 161%) and overall predictive value of 69% for venlafaxine, which was mainly driven by a small subgroup (N = 9) of patients receiving psychopharmacotherapy only (PPV = 75%, nPPV = 225%, and overall predictive value = 89%).

RTMS 1-HZ AND CONCURRENT PSYCHOTHERAPY

Another independent out-of-sample validation was conducted, consisting of 36 MDD patients receiving 1-Hz rTMS + PT with a group remission rate of 47% (dataset 6). Remission prediction based on the posterior alpha network in a blinded fashion resulted in a PPV of 31.6% (nPPV = 66.9%).

THE SIGNIFICANCE OF THE POSTERIOR ALPHA NETWORK

To explore a possible relationship between the network and other variables, bivariate correlation analyses between posterior alpha network score and baseline variables resulted in significant correlations ($p < 0.001$) at $\rho > 0.1$ with age ($\rho = 0.381$), hours of sleep ($\rho = -0.251$), oddball false negatives ($\rho = -0.146$), oddball false positives ($\rho = -0.144$) and the personality trait extraversion ($\rho = -0.107$). All correlations, except for age, were driven by children and teenagers (age <18 years) and became nonsignificant in adults only, or when (partial correlation) analyses were covaried for age. The Spearman's rank correlation coefficient for age was equal in adults ($\rho = 0.196$) and nonadults ($\rho = 0.192$), but larger in male ($\rho = 0.462$) compared to female ($\rho = 0.237$) patients for all ages (see figure 2C). Reliability analysis yielded an ICC of 0.976 (95% confidence interval 0.974-0.977). One-way repeated measures ANOVA showed only a significant main effect of age group ($F = 71.4$; $p < 0.001$) and effect of time on age ($F = 1.72$; $p = 0.005$; see figure 2D), and no effects of sex ($p > 0.05$). Finally, a follow-up correlation analysis to explore a time effect revealed no significant correlation ($p < 0.001$) between baseline variables and the slope of ten consecutive timeframes. Nor was a significant difference between the first and last timeframe for both sexes detected.

DISCUSSION

In this study we identified a posterior-alpha ageing brain network that was associated with remission to two different evidence-based treatments for MDD, in a drug-class specific and sex-specific manner, providing potential for treatment stratification purposes (Arns et al. 2022). The network was significantly associated with remission to venlafaxine, resulting in a nPPV of 138%, as well as rTMS + PT, but in the opposite direction for women relative to men, yielding an overall nPPV of 131%. Remission to venlafaxine was associated with a high network score in both women and men, while this association was not found for escitalopram or sertraline. Drug-specific EEG associations have been uncovered before. For example, EEG abnormalities were shown to be associated with drug-specific nonresponse to venlafaxine and escitalopram, but not sertraline (Arns, Gordon, and Boutros 2017), while left frontal alpha asymmetry in women is related to poorer response to both escitalopram and sertraline, but not to venlafaxine (Arns et al. 2016). Although mechanistic insights into the biological underpinnings of EEGs are largely unknown, our findings hint that activity in this network may be related to antidepressants' mode of action, since venlafaxine is a reuptake inhibitor of both serotonin and norepinephrine, while the other two antidepressants selectively inhibit serotonin.

Remission to rTMS + PT was differentially associated with a high network score in men and low network score in women, but neither rTMS protocol (1- or 10 Hz) specific association was found nor an effect for a psychotherapy only sample, suggesting the effects to be general to rTMS. These findings hint at different underlying mechanisms of action of rTMS on neural activity for men compared to women, which is supported by prior research reporting an opposite pattern regarding posterior alpha asymmetry in men and women with MDD (Stewart et al. 2011), and sex-specific differences in rTMS response (Huang et al. 2018; Kedzior, Azorina, and Reitz 2014; Sackeim et al. 2020). Out-of-sample validation confirmed our findings for venlafaxine, but not for rTMS. This inconsistency may be related to the relatively small sample size of available data (given male and female predictions were in opposite directions, effectively

halving the available sample) and thus the rTMS finding awaits confirmation in future samples.

The posterior alpha network we described explained >60% of the total signal variance of the EEG and was reflective of alpha oscillations in the parietal lobe, and inversely related to alpha oscillations in the occipital lobe. A high network score was related to parietal/midline alpha activity and a low score to occipital activity, thus an increase in network score from low to high may reflect a shift of alpha power from posterior to more anterior cortical locations. This finding supports prior research showing that cortical maturation, which consists of an increase of faster oscillatory activity (including alpha) together with a decrease of slow activity, proceeds strictly from posterior to anterior regions, probably indicating a decrease in magnitude of posterior alpha rhythms during physiological aging (Mason, Barry, and Clarke 2022; Clarke et al. 2001a; Chiang et al. 2011; Babiloni et al. 2006).

Post-hoc, we found a robust positive correlation between the posterior alpha network score and age, but no other baseline variables in adults (after co-varying for age effects). Correlations with sleep, false negatives and positives on the oddball test and extraversion were all negative and driven by young patients and age. It is possible that some or all of these variables, such as sleep, are actually age-dependent, rather than directly related to the network.

In previous studies, higher age has been associated with non-response to various treatments, including rTMS, possibly mediated by treatment-resistance and episode recurrence, but results remain inconclusive (Carlo, Calati, and Serretti 2016; Aoun et al. 2022; Figiel et al. 1998; Krepel et al. 2019). Our results cannot be simply explained by age, because of several factors. First, we controlled for age in all analyses. Second, no significant age differences were found between remitters and nonremitters. Third, age was not a mediator of the relationship between the network score and venlafaxine treatment- or rTMS outcome in women. However, there was a mediation effect of age with regards to rTMS outcome in men. Looking into the relation between age and network score on the one hand, and age and rTMS

response on the other, we found that male responders had a higher mean network score and were on average younger than nonresponders. This is the opposite of what is expected, since a higher network score was related to a higher age.

Differences in (overall) EEG alpha power and (frontal as well as posterior) alpha asymmetry between responders and nonresponders to antidepressants have been described, suggesting alpha activity is a biological substrate for clinical response in patients with MDD (Tenke et al. 2011; Bruder et al. 2008; Bruder, Tenke, and Kayser 2013; Bruder et al. 2001). A previous study using LORETA found increased alpha activity in depressed patients at parietal and occipital sites (Grin-Yatsenko et al. 2010), which is consistent with other studies describing an (asymmetric, mostly right-hemispheric) elevated alpha in posterior regions in adult depressed patients (Flor-Henry, Lind, and Koles 2004; Henriques and Davidson 1990; Fingelkurts et al. 2006). All these findings highlight the implication of age-related and sex-specific posterior alpha power alterations for depression and antidepressant treatment effects.

The alpha network described here showed only few similarities with the functional brain network identified in our proof-of-concept study (Meijs et al. 2022), that was a sex-specific, nontreatment-specific, one-directional predictor for treatment outcome in male MDD patients. Here, the most prominent observed oscillatory network activity were diffuse cortical slow wave (delta and theta) oscillations. Activity within higher frequencies (including alpha) was solely present at left occipital regions. The differences may be the result of differences between eLORETA-fICA datasets. The sample in the present study is four-fold larger and includes the full lifespan instead of adults only. Moreover, while both samples are heterogeneous, the psychiatric background of patients in both samples partly differs (in-patients vs. out-patients). Another explanation is the use of high-density EEG for eLORETA-fICA in the previous study, resulting in less well-defined spatial components, hampering interpretation.

A theory of the pathogenesis of MDD that is supported by prior research under resting conditions proposes the regulation of wakeful

EEG-vigilance stages –which is considered to be a state-dependent trait (Hegerl et al. 2008)– is 'hyperstable' in depression. MDD patients show less (and later) declines into lower EEG-vigilance stages than healthy controls, which was even observed in a relative short eyes-closed period of two minutes (Hegerl et al. 2011; Ulke et al. 2018). Furthermore, arousal parameters have been associated with response to antidepressant medication and seem to be potential biomarkers for the improvement of MDD treatment outcome (Olbrich et al. 2016). In line with the vigilance/arousal hypothesis in MDD, we examined whether the posterior alpha network score changed over ten EEG recording intervals within two minutes, and whether it was predictive of the stage of vigilance that could explain the association of the network score with the antidepressant outcome. The network was found to be highly stable over time, as demonstrated by the very high ICC = 0.98. The stability of the posterior alpha network and its association with genetics indicates this network is a trait rather than a state feature. Prior research found that posterior EEG alpha amplitude at rest is temporally stable in adulthood and therefore indicative of an individual trait (Tenke et al. 2018). On the other hand, since we found a relation with age which suggests the alpha network is a state characteristic, it may also reflect neurodevelopmental characteristics, with possible predictive value for lifetime depression and treatment outcome. A recent study that supports this hypothesis found increased posterior alpha asymmetry, but reduced overall alpha power in depressed female adolescents, suggesting developmental dissimilarities regarding the posterior alpha-MDD relationship, suggesting that alpha oscillations are more variable during periods of neurodevelopment and a promising neurophysiological indicator of MDD in adolescents (Umemoto et al. 2021). More research into underlying EEG characteristics in different patient groups and healthy controls is warranted for examining the clinical predictive value of these measures and evaluating whether brain arousal is particularly characteristic for responders to antidepressant treatment.

Strengths of this study include the use of multiple large independent samples, as well as a lifespan perspective and combining genetics with a neurophysiology approach, and the blinded out-of-sample validations in independent samples. We used a heterogeneous dataset,

that consisted of patients with various psychiatric disorders across a broad age spectrum. This allowed for a data-driven data-reduction into independent components, and subsequent PGS-informed selection of one component that would be transdiagnostic and translate better to a normative dataset, rather than a dataset of adult MDD patients only. Moreover, the eLORETA-fICA method is applicable to all EEGs independent of amplifier, electrode configuration or number of electrodes. However, the interpretation of the functional networks obtained is difficult and limited by visualization of neural activity with low resolution and within predefined frequency bands. Other limitations of the present study include the relatively small sample sizes for the out-of-sample validations and the lack of a placebo-controlled arm as part of the open label setup. However, the opposite effects for men and women in the rTMS group argue against a notion of placebo-effects. We were able to replicate the findings for venlafaxine, but not for rTMS + PT. A possible reason for this lack of replication could be the lack of power due to the small sample sizes (mainly as a result of dividing samples based on sex and remission versus nonremission), and a mediation effect of age in men. A future larger sample is required to validate the findings. Also, the out-of-sample rTMS + PT sample consisted of patients receiving only 1 Hz rTMS and thus results must be interpreted with caution and require further study. Finally, the network was significantly associated with remission to venlafaxine, but not the two SSRIs included in our study. However, stratification of the full medication sample resulted in an nPPV of 112%.

In conclusion, we identified a highly stable EEG posterior alpha network that is related to polygenic liability for antidepressant response as well as age, and is associated with remission to two evidence-based treatments for MDD.

SUPPLEMENTARY INFORMATION

SUPPLEMENTARY METHODS AND MATERIALS

EEG RECORDINGS

During eyes-closed EEG recordings, the participants were instructed to sit still for the duration of the recording without thought instructions. EEG data of TDBRAIN+ (dataset 1) were acquired for two minutes from 26 channels, based on the 10–10 electrode international system using a Compumedics Quickcap or ANT-Neuro Waveguard Cap with sintered Ag/AgCl electrode, at a sampling rate of 500 Hz. The EEG was recorded with a virtual ground and offline referenced to averaged mastoids (A1 and A2) with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. EEG recordings for dataset 2 were acquired from 65 channels of the Electrical Geodesics Incorporated (EGI; Magstim, UK) system, and were recorded for three minutes during eyes closed condition (see Meijs et al. (Meijs et al. 2022) for further details). The acquisition of two-minutes resting-state EEG recordings of the other datasets from a 26-channel system of the Neuroscan NuAmps (Compumedics, Australia) was similar to the EEG recordings of TDBRAIN+.

OTHER DATA TDBRAIN+

In addition to the raw EEG recordings, the TDBRAIN+ database (for more information see Van Dijk et al. (Van Dijk et al. 2022)) also contains demographic and clinical (such as the results from questionnaires) data, and behavioral measures (such as the results from an auditory oddball task) that were performed after the resting-state conditions. For the oddball task participants were presented with a series of low- (500 Hz) and high- (1000 Hz) pitched tones (50 ms, 75 dB) with an interstimulus interval of 1 s. Participants were instructed to respond to the high pitched 'target' tone (60 targets out of 340 stimuli) with both index-fingers.

SUPPLEMENTARY RESULTS

RESULTS FOR RESPONSE

Supplementary results for venlafaxine. We performed an ANCOVA with EEG component score as dependent variable and response and sex as fixed factors, and age and baseline QIDS as covariates. This yielded a significant ($p = 0.026$) response × type of antidepressant interaction. Repeating the analysis with response as fixed factor for SSRIs and SNRIs separately resulted in a main effect of response for venlafaxine ($d = 0.352$, $F = 6.948$, $p = 0.009$), but not for escitalopram or sertraline. A discriminant analysis was performed within the venlafaxine group; the EEG component 1 alone significantly predicted response ($\lambda = 0.970$, $\chi^2 = 4.759$, $p = 0.029$).

Supplementary results for repetitive transcranial magnetic stimulation (rTMS). We performed an ANCOVA with EEG component score as dependent variable and response and sex as fixed factors, and age and baseline BDI-II as covariates. This yielded a significant ($p < 0.001$) response × sex interaction; no protocol interaction. Repeating the analysis with response as fixed factor for men and women separately resulted in a main effect of response for men ($d = 0.499$, $F = 12.871$, $p < 0.001$), and women ($d = -0.597$, $F = 6.894$, $p = 0.010$). A discriminant analysis was performed and revealed that the EEG component 1 as single predictor significantly predicted response ($\lambda = 0.939$, $\chi^2 = 5.702$, $p = 0.017$) in women. For men the predictive value was in the other direction for both response ($\lambda = 0.938$, $\chi^2 = 5.751$, $p = 0.016$).

RESULTS HELD-OUT OF SAMPLE VALIDATION

We performed an out-of-sample validation in a held-out sample as a first-level validation, where the validation in an independent dataset was considered a second-level validation to ensure robustness. Therefore, within dataset 3 and 4 we determined the optimal cut-off in a training set (~70% of patients, randomly selected), which resulted in a PPV of 47% (nPPV = 137%) for venlafaxine and 70% (nPPV = 125%) for rTMS, and replicated these findings in the validation set (the remainder ~30% of patients): PPV=50% (nPPV = 142%) for venla-

faxine and PPV = 80% (nPPV = 145%) for rTMS.
Note: results for venlafaxine were also replicated in an independent dataset, while this was not the case for rTMS. With regard to the rTMS samples (dataset 4 and 6), we did not expect considerable differences between these samples, since both were obtained from the same clinic and had a fairly heterogeneous patient population with comorbidities. However, there might be some confounding differences, such as difference in number of sessions.

SUPPLEMENTARY FIGURES AND TABLES

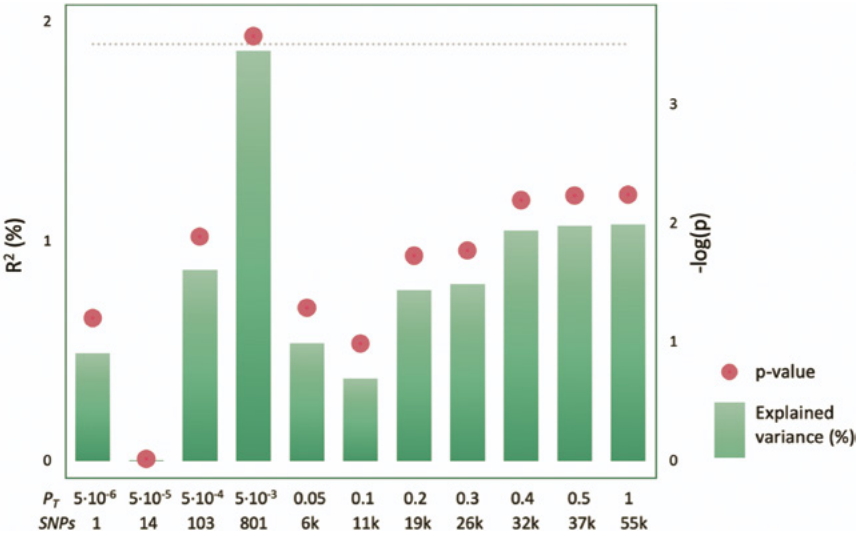


Figure S1. *Polygenic regression model for antidepressant response. The graphs show the explained variance (R^2 as %) of the individual score on EEG component 1 by PGS-AR (polygenic score for antidepressant response [improvement]; blue bars), and corresponding p-value (presented as -log; orange dot) on the x-axis per p-value threshold (P_T) on the y-axis. The Bonferroni-corrected significance level is also presented (α, grey dotted line). The graph shows a polygenic signal: the more lenient the P_T is, the more variance is explained by the PGS-AR (and the more significant its p-value is: $p < 0.01$ for $R^2 > 1\%$) in general. The optimal P_T survives Bonferroni-correction ($P_T < 5 \cdot 10^{-3}$, $R^2 = 1.90\%$).*

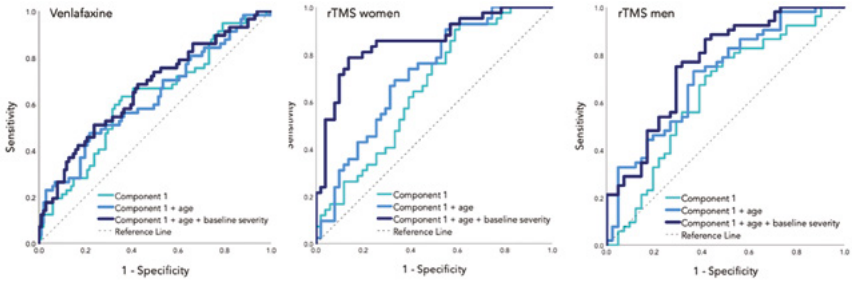


Figure S2. *Receiver operating characteristic (ROC) curves for treatment remission. ROC curves are plotted for male and female depressed patients treated with venlafaxine (A), and for rTMS in women (B) and in men (C) with MDD. The colors represent different predictive models. The first model (light blue) shows the discriminative performance of the EEG component 1 alone, the second improved model (blue) shows the performance when age is added as predictor, and the third model (dark blue) represents the most optimal model including all three predictors: component 1, age and baseline depressive symptom severity. Note that the model minimally improves after adding age and baseline severity successively to the model as regards to venlafaxine, while the model clearly improves for rTMS after adding these predictors*

A

		True remission		
		0	1	Total
Predicted	0	68	21	89
	1	39	36	75
Total		107	57	164

B

		True remission		
		0	1	Total
Predicted	0	60	42	102
	1	23	61	84
Total		83	103	186

Table S1. Cross tables: prediction based on network score cut-offs for remission.
Cross tables for remission based on optimal cut-offs for venlafaxine (A) and rTMS/psychotherapy (B).
0 = no remission; 1 = remission.

.

4

A DEEP LEARNING DERIVED TRANSDIAGNOSTIC EEG SIGNATURE INDEXING HYPOAROUSAL AND IMPULSE CONTROL: IMPLICATIONS FOR TREATMENT PREDICTION IN ADHD AND MDD

ABSTRACT

Psychiatric disorders are traditionally classified within diagnostic categories, but this approach has limitations. Research Domain Criteria (RDoC) constitute a research classification system for psychiatric disorders based on dimensions within domains that cut across these psychiatric diagnoses. The overall aim of RDoC is to better understand mental illness in terms of dysfunction in fundamental neurobiological and behavioral systems, leading to better diagnosis, prevention and treatment. A unique electroencephalographic (EEG) feature, referred to as spindling excessive beta (SEB), has been studied in relation to impulse control and sleep, as part of the arousal/regulatory systems RDoC domain. Here, we study EEG frontal beta activity as a potential transdiagnostic biomarker capable of diagnosing and predicting impulse control and sleep problems. We show in the first dataset (N = 3,279) that the probability of having SEB, classified by a deep learning algorithm, is associated with poor sleep maintenance and low daytime impulse control. Furthermore, in two additional, independent datasets (iSPOT-A, N = 336; iSPOT-D, N = 1,008), we revealed that conventional frontocentral beta power and/or SEB probability, referred to as Brainmarker-III, is associated with a diagnosis of attention deficit hyperactivity disorder

(ADHD), with remission to methylphenidate in children with ADHD in a sex-specific manner, and with remission to antidepressant medication in adults with a major depressive disorder in a drug-specific manner. Our results demonstrate the value of the RDoC approach in psychiatry research for the discovery of biomarkers with diagnostic and treatment prediction capacities.

INTRODUCTION

Psychiatric disorders are often conceptualized as classifications on the basis of symptoms, defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM (APA 2013)). This approach of classifying patients into diagnostic categories provides benefits such as reliability and a common terminology. However, The National Institute of Mental Health proposed the Research Domain Criteria (RDoC) as a research classification system for mental disorders (Cuthbert and Insel 2013). This system is built on fundamental dimensions of neurobiology and behavioral systems, which differ from and cut across the existing DSM-5 categories that do not adequately reflect these systems. RDoC aims to enhance our understanding of mental health by considering subthreshold symptoms and enabling research into the underlying systems. This approach allows for a more nuanced and multi-dimensional perspective on mental illness, facilitating improved diagnosis, prevention, and treatment through a comprehensive exploration of dysfunction across various dimensions. The five domains of RDoC include dimensions that can be measured and provide constructs for validation. Moreover, they are all transdiagnostic, as disruptions in these dimensions could be observed in psychiatric patients independent of their DSM classification. In a prior study from Arns et al. (Arns, Swatzyna, et al. 2015), researchers looked into the relationship between dimensions of the arousal/regulatory domain of the RDoC within a large, heterogeneous outpatient psychiatric population. The results indicated that sleep maintenance problems mediate impulse control, which is, in turn, associated with a unique electroencephalography (EEG) feature called spindling excessive beta (SEB). Furthermore, SEB is most likely

a consequence of the sleep problems. Therefore, this study concludes that frontocentral SEB could be considered a state marker caused by sleep difficulties with concurrent impulse control problems.

Frontocentral SEB is defined as synchronous activity in the beta range that is characterized by its spindle morphology with an anterior emphasis (Johnstone, Gunkelman, and Lunt 2005). Relatively little is known about (excessive) beta spindling. It is observed as a medication effect, particularly of sedatives, such as benzodiazepines (Johnstone, Gunkelman, and Lunt 2005; Blume 2006). Oscillatory activity in the beta range (15-25 Hz) is generally known to reflect a state of alertness or hyperarousal, supported by its association with attention, perception and cognition. Furthermore, elevated beta activity levels observed in patients with insomnia suggest that insomnia may be characterized by central nervous system hyperarousal (Perlis et al. 2001). Frontocentral SEB, however, might be a reflection of hypoarousal, which is supported by an early study that found beta spindles to occur during drowsiness and in sleep stage 1 (Kubicki and Ascona 1983).

The association between the presence of SEB and impaired impulse control levels was replicated in a recent study, encompassing attention-deficit/hyperactivity disorder (ADHD) and insomnia patient groups, implying that SEB serves as a marker for impulse control problems (Krepel et al. 2021). Interestingly, a relation between sleep and frontocentral SEB could not be established in this study using subjective questionnaires for sleep problems.

The ADHD group is of particular interest as a study population in the context of impulse control problems, because impulsivity is one of the primary symptoms of ADHD, and children or adults are only diagnosed if they show sufficient primary symptoms (APA 2013). Prevalence rates of (spindling) excessive beta range between 13 and 20% in the ADHD population (Chabot and Serfontein 1996; Clarke et al. 1998; 2001c) and evidence suggests that these patients respond well to stimulant medication (Chabot et al. 1999; Clarke et al. 2003). A study of children with ADHD and matched healthy controls, demonstrated that the prevalence of different EEG phenotypes

was comparable between the two groups, including frontocentral SEB (Arns et al. 2008). Although this study was based on a relatively small and heterogenous sample, the findings suggest SEB might be a transdiagnostic EEG phenotype.

Another psychiatric disorder of interest in the context of impulsivity is major depressive disorder (MDD). Although impulsivity is not a symptom of MDD according to the DSM, it is a heterogenous psychiatric disorder and several prior RDoC studies have proposed a cognitive subtype of MDD (Etkin et al. 2015; Hack et al. 2023). Hence, we include MDD to examine how impulse control (a cognitive process) could potentially influence our understanding of the heterogeneity within MDD.

SEB as a transdiagnostic marker has an important weakness: it is a subjective marker as the classification of SEB depends on visual inspection of the EEG. This is time-consuming with possibly low inter-rater reliability. The first aim of the present study was therefore to automate and operationalize SEB as we have done in previous work (Putten, Olbrich, and Arns 2018). Here, we used a 'top-down and bottom-up' approach to operationalize SEB. Top-down we performed a data-driven data-reduction analysis at source level activity, which was not limited to the beta range but includes 0.5 to 30 Hz oscillations. This broad spectral range was chosen for validation that impulse control is associated with frontal beta activity. Bottom-up we tested two operationalizations for frontal beta activity as potential transdiagnostic biomarker: conventional frontocentral beta power and a deep learning model classifying frontocentral SEB ('Brainmarker-III'). Secondly, in the 'mechanistic validation phase' (Hartung, Hoffmann, and Stephens 2013), we focused on replicating the beforementioned relation between frontal beta activity, sleep and impulse control, to better understand the underlying biological mechanism of this triangular relationship (Arns, Swatzyna, et al. 2015). Then, in the 'translational phase', we explored potential diagnostic and prognostic capabilities of frontal beta activity, as this is of important clinical relevance. The latter phase involved three different samples: one including children with ADHD, two including adults with MDD. Finally, we combined these predictions to develop Brainmarker-III. Prior work

already developed an individual alpha peak frequency (iAPF) based treatment stratification biomarker (Brainmarker-I), which aids to differentially inform stratification to two ADHD treatments and various antidepressant treatments in MDD (Voetterl et al. 2023; Voetterl et al. 2022). Furthermore, frontal alpha asymmetry (Brainmarker-II) is a differential predictor of antidepressant response robust to state and drug effects (Van der Vinne et al. 2019). The final goal of this study was to explore the diagnostic and treatment predictive capabilities of Brainmarker-III within ADHD and MDD cohorts.

METHODS AND MATERIALS

DATASETS

DATASET 1

This dataset consists of data obtained from the Two Decades-Brainclinics Research Archive for Insights in Neurophysiology (TDBRAIN), supplemented with data from other clinics that used identical recording details (TDBRAIN+), and contains clinical lifespan (5-89 years) resting-state eyes-closed EEG data complemented with relevant clinical and demographic data of a heterogeneous collection of patients and healthy participants. The dataset (version 7) includes 4,691 participants in total (mean age: 30.33 ± 18.18; 61% adult; 57% male). A subsample of MDD patients treated with transcranial magnetic stimulation (TMS; see dataset 4 below) was used for the translational analysis, thus these data were excluded from the development phase. The open access TDBRAIN dataset is freely available at www.brainclinics.com/resources, with all data recorded at Research Institute Brainclinics (Brainclinics Foundation, Nijmegen, The Netherlands (Van Dijk et al. 2022)). All participants (or their guardians when underaged) provided written informed consent.

Data for discovery/exploration of EEG parameters with predictive capacity concerning impulsivity consisted of a heterogenous sample obtained from the TDBRAIN+ (Impulsivity sample), which included all participants of whom complete task data for the continuous performance task (explained later) were available (N = 3,279; mean age:

29.5 ± 17.5; 61.5% adult; 59% male). Data for transdiagnostic mechanistic validation also consisted of a sample from the TDBRAIN+ (Actigraphy sample), and included all adults of whom actigraphy measurements were available. This resulted in a sample of adult patients with a variety of (psychiatric) disorders, but the majority consisted of ADHD, MDD, obsessive-compulsive disorder and insomnia. The Actigraphy sample partly overlapped with the Impulsivity sample (41%), as for these participants both impulsivity and actigraphy data were available.

DATASET 2

This sample was obtained from the international Study to Predict Optimized Treatment for ADHD (iSPOT-A), an international, multi-center, prospective open-label trial, which enrolled 336 children and adolescents with a formal diagnosis of ADHD (mean age: 11.9 ± 3.3; 73% male) and 158 healthy children (mean age: 12.2 ± 3.2; 71% male). Data were used for translational purposes. Symptom severity was established at baseline and after six weeks of treatment with methylphenidate using the clinician rated ADHD Rating Scale IV (ADHD-RS-IV). All guardians of the participating children provided written informed consent. Details about this sample have been published elsewhere (Arns et al. 2018).

DATASET 3

This sample was obtained from the international Study to Predict Optimized Treatment in Depression (iSPOT-D), an international multi-center, randomized, prospective open-label trial (phase-IV clinical trial). This study, also included for translation of findings to symptom severity and treatment response, consisted of 1008 patients (mean age: 38.6 ± 12.6; 58% female) diagnosed with non-psychotic MDD who were randomized to one of the selective serotonin reuptake inhibitors escitalopram or sertraline, or to the serotonin and norepinephrine reuptake inhibitor venlafaxine. The study protocol was approved by the institutional review boards at all of the participating sites and this trial was registered with ClinicalTrials.gov under

id NCT00693849. All participants provided written informed consent. At baseline and after eight weeks of treatment patients filled in the Quick Inventory of Depressive Symptomatology (QIDS). For treatment response analysis, only data from participants who completed eight weeks of randomized medication treatment ('per protocol' sample) were included. Details about this sample have been published elsewhere (Arns et al. 2016).

DATASET 4

This sample of 196 patients (mean age: 43.2 ± 12.9; 51% female) were diagnosed with non-psychotic MDD and were treated with high-frequency TMS (10-Hz left dorsolateral prefrontal cortex, DLPFC) or low-frequency TMS (1-Hz right DLPFC); a minority received both 1-Hz and 10-Hz sequentially. This dataset is part of the TDBRAIN+. All patients completed at least ten sessions of treatment and completed the Beck Depression Inventory II (BDI-II) at baseline and at the last session (on average session 21). Concurrent with TMS, patients received psychotherapy. Details about this sample are described elsewhere (Krepel et al. 2019).

EEG RECORDINGS

All resting-state eyes closed EEG recordings (two minutes) were acquired from the same hardware platform using a 26-channel system of the Neuroscan NuAmps, Quickcap or ANT-Neuro Waveguard Cap (Compumedics, Australia) at a sampling rate of 500 Hz. During the recordings subjects were instructed to close their eyes, sit still and relax. Data were recorded by the following electrodes: Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, C3z, C3, C4, CPz, CP3, CP4, Pz, P3, P4, P7, P8, T7, T8, Oz, O1, O2. Electro-oculography (EOG) was measured by electrodes placed 3 mm above the left eyebrows and 1.5 cm below the left bottom eye-lid, and 1.5 cm lateral to the outer canthus of each eye respectively.

EEG PRE-PROCESSING AND ANALYSIS

For cleaning of the TDBRAIN+ data, a previously published automatic pre-processing pipeline (in Python) was used that is described by Van Dijk et al. (Van Dijk et al. 2022); available for download at www.brainclinics.com/resources. In short, EEG data was demeaned and bandpass-filtered between 0.5 to 100 Hz and the notch-frequency of 50 Hz was removed. The bipolar EOG was computed and blinks were removed from the EEG data using a regression method (Gratton, Coles, and Donchin 1983). Artifact signals were detected and if a channels' signal contained artifacts for more than 66% of the measurement it was repaired using a Euclidian distance weighted average of at least three neighboring channels. Data were divided into 2-second segments for frequency analysis and training the deep learning algorithm. Data where >66% of segments contained artifacts were discarded from further analysis.

FUNCTIONAL NETWORK ANALYSIS (TOP-DOWN)

A functional independent component analysis (fICA), was performed in a prior study using exact Low Resolution Brain Electromagnetic Tomography (eLORETA) for estimating the cortical source distribution of electric neuronal activity, as described by Meijs et al. (Meijs et al. 2024). In this case, data were divided into 4-second segments. The eLORETA method is a discrete, three-dimensional (3D) distributed, linear inverse solution, with the property of exact localization to test point sources, yielding images of current density with exact localization, albeit with low spatial resolution (Pascual-Marqui 2007). By means of eLORETA-fICA, previously described as a data-driven data-reduction approach (Meijs et al. 2022; Gerrits et al. 2019; Meijs et al. 2024), a total of 54 components (i.e. functional networks), within a bandwidth ranging from the delta to gamma frequency band, were extracted from a sample (N = 4,045) obtained from TDBRAIN+. Every participant received a score (or component weight) for each functional network, indicating how active a specific network is in that participant. For each subject in each dataset, 54 component scores were obtained, which were used in the statistical analyses.

DEVELOPMENT OF BRAINMARKER-III (BOTTOM-UP)

Two metrics were tested as potential objective transdiagnostic impulsivity biomarker (Brainmarker-III).

1. **Frontocentral average beta power.** The oscillatory power in the beta-range (14.5 to 30 Hz, on 2-second artefact-free segments) was calculated using the python package MNE-Python (Gramfort et al. 2013). Power in this band was computed for nine frontocentral electrodes (F3, Fz, F4, FC3, FCz, FC4 C3, Cz and C4) using a multitaper analysis with 7 cycles and a time-bandwidth of 2. The absolute mean beta power over these nine electrodes, averaged over all artifact-free segments, was calculated. We will use the term "beta power" to denote this metric.
2. **SEB probability.** To develop an algorithm that could detect frontal SEB, a convolutional neural network (CNN) model was trained since that type of model previously was successfully used for the analysis of EEG in several studies (Tjepkema-Cloostermans, Carvalho, and Putten 2018; Putten, Olbrich, and Arns 2018). See Supplementary Methods for details on the development of this model. If >5% of the segments (prominence) had >50% chance (probability) of containing SEB, a participant's EEG was classified as containing SEB. The model was able to classify participants EEGs containing SEB with an average accuracy of 0.70, a sensitivity of 0.78 and a specificity of 0.70. For the current study the automatically classified average segment probability of containing SEB per subject was used as feature in the following analyses.

OBJECTIVE BEHAVIORAL MEASUREMENTS

To prevent (self) reporting bias (including possible differences between disorders due to different questionnaires) we focused on objective behavioral measures to operationalize impulse control and sleep problems. Impulse control was defined by false positive (FP) errors (commission errors) on a continuous performance task, obtained from a visual 1-back working memory (WM) task (Van Dijk et al. 2022), performed after the resting state conditions. The number of FP errors on the WM task (WM-FP) was used as continuous measure. For dichotomous tests, participants were considered to have low impulse control at WM-FP > 1 and normal impulse control at

WM-FP = 0 (similar to prior work (Gerrits et al. 2019)). Datasets with >15 WM-FP were considered outliers (who misunderstood task-instructions) and removed. Sleep maintenance problems – including wake after sleep onset (WASO) and number of awakenings during sleep – were objectively assessed by actigraphy (Actiwatch, Condor ActTrust), assessed for at least 7 days prior to treatment.

STATISTICAL ANALYSES

All analyses were performed using IBM SPSS Statistics 27. Age was added as a covariate where appropriate. If effects between male and female participants were significantly different or in opposite direction, analyses were performed stratified by sex. Sensitivity analyses within subgroups (males, females, adults or children) were performed to reveal sex-specific and age-specific differences that could potentially average out main effects on the total sample.
Since the data were not normally distributed, non-parametric correlation analysis (Spearman) was performed to asses associations. The statistics of the main analyses were corrected for the number of tests (Bonferroni), and for significant effects, effect sizes were computed. The significance level for follow-up analysis was set at $\alpha = 0.05$. The a priori set hypothesis was that EEG beta measures were associated with impulse control problems on the one hand and sleep maintenance problems on the other.

First (discovery/exploration phase), we examined whether there was an association between impulse control and one of the 54 networks derived from the aforementioned eLORETA-fICA analysis (top-down) for validation purposes. The eLORETA-fICA was not used in subsequent analyses. A One-Way ANCOVA, with age as a covariate, was conducted to investigate differences in beta power and SEB probability between individuals with low and normal impulse control. Correlation analyses between WM-FP and the two metrics, were done in addition to the binary tests.
Second (mechanistic validation phase), we focused on sleep maintenance problems (WASO and awakenings) within the Actigraphy sample, and investigated the triangular relationship of impulse control, sleep and frontal beta activity using correlation analyses.

Third (translation phase), analysis focused on translating the findings for diagnostic or prognostic use. Therefore, the associations between beta power or SEB probability and baseline clinical data (ADHD-RS-IV for ADHD and QIDS or BDI-II for MDD) were analyzed using Spearman correlation analyses. An ANCOVA was performed to confirm a difference in SEB probability between children with and without ADHD. In addition, we examined associations between both beta power and SEB probability as dependent variables and categorical outcomes as fixed factors (remission and response, sex, antidepressant and TMS protocol), controlling for age and baseline symptom severity (based on ADHD-RS-IV, QIDS or BDI-II). Remission was the primary outcome, defined as ≤18 on the ADHD-RS-IV for ADHD, and ≤5 on the QIDS or ≤12 on the BDI-II for depression. Response was the secondary outcome, defined as ≥50% improvement from baseline on the self-rated questionnaires. If both variables were associated with diagnosis or remission, a prediction model with both variables was developed to investigate if a combination of the variables was more predictive of diagnosis or remission than each independent variable. All treatment outcome analyses were performed per protocol.

Lastly, for the development of Brainmarker-III, different cut-off points were established based on the highest Youden index for beta power and SEB probability, and the positive predictive value (PPV) and normalized PPV (nPPV; defined as subsample improved remission rate) were calculated.

RESULTS

DISCOVERY/EXPLORATION PHASE

FRONTAL BETA NETWORK (FICA)

Low impulse control was associated with a significantly higher score of network 44 ($F = 11.83$, $p = 0.0006$, $d = 0.236$), out of 54 functional networks. The effect was in the same direction for men and women, and for children and adults. No significant associations were found with other networks. Figure 1 visualizes the activity of network 44, which is a (left-sided) frontal beta network, confirming the associa-

tion between beta power and impulse control, and a small anti-correlated delta-theta component right-temporal. It also shows that the contrast between high and low network score in the beta band is located at the frontal midline (two-sided).

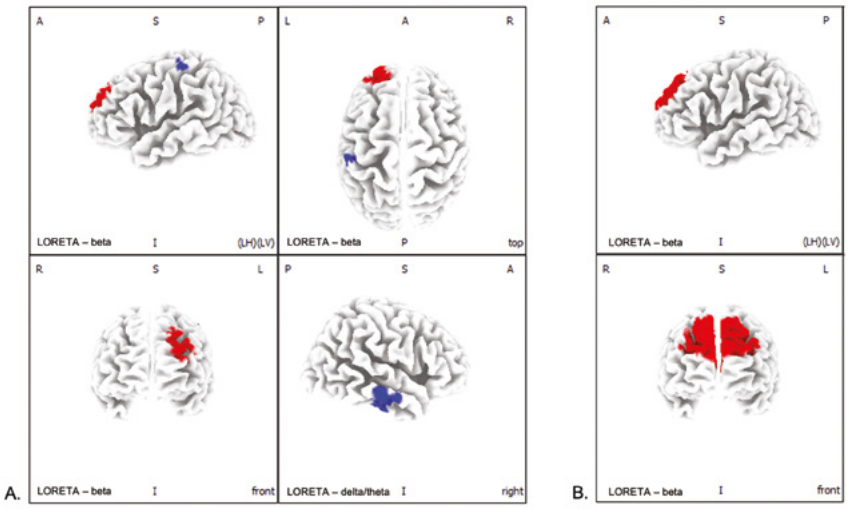


Figure 1. *The frontal beta network (EEG component 44) using eLORETA-fICA. The left map (A) visualizes this network viewed from four different angles (anterior [A], posterior [P], superior [S], inferior [I], left [L], left view [LV] and left hemisphere [LH]). The two colors represent joint neural activation and deactivation (anticorrelation). The component covers left-sided beta activity at the (anterior and dorsolateral) prefrontal cortex (red; Brodmann area [BA] 9 and 10), anticorrelated to beta activity in a small area of the left primary somatosensory cortex (blue), as well as right-sided slow-wave (delta/theta) activity at the temporal cortex (blue; BA 20 and 21), which is also anticorrelated to left-sided prefrontal beta activity. The right map (B) visualizes the significant difference between participants with the highest frontal beta network score (N = 500) versus the lowest score (N = 500) from two different angles (note: for simplification only beta activity is showed). This illustrates the clear contrast between high versus low network score: a high score is associated with frontal midline beta activity, and not only left sided beta activity as the network suggests.*

FRONTOCENTRAL BETA POWER

Low impulse control was associated with a significantly higher beta power ($F = 26.93$, $p < 0.00001$, $d = 0.180$). A sensitivity analysis indicated that the effect was in the same direction for both men and women, statistically significant in adults only ($F = 9.47$, $p = 0.002$, $d = 0.171$), with no significance observed in children. There was also a small, significant positive correlation between WM-FP and beta power ($\rho = 0.098$, $p = 0.0005$) in adults.

SEB PROBABILITY

Low impulse control was associated with a significantly higher SEB probability ($F = 10.01$, $p = 0.002$, $d = 0.033$). A sensitivity analysis indicated that the effect was in the same direction for both men and women, statistically significant in adults only ($F = 4.748$, $p = 0.030$, $d = 0.112$), while there was no effect in children. In adults, there was a small, significant positive correlation between WM-FP and SEB probability ($\rho = 0.060$, $p = 0.034$).

CORRELATION OF EEG PARAMETERS

Beta power was significantly, but weakly, correlated to SEB probability ($\rho = 0.367$) and the frontal beta network ($\rho = 0.170$) at $p < 0.00001$. However, there was no correlation between SEB probability and the frontal beta network.

Although there is a correlation between beta power and SEB probability, the degree of overlap is modest. Associations were identified, affirming that more impulse control problems are linked to both beta power and SEB probability, but the effect sizes appear small. Consequently, in the subsequent phase, we delved deeper into this relationship with a mechanistic validation, exploring the potential involvement of sleep maintenance.

SLEEP MAINTENANCE PROBLEMS AS TRANSDIAGNOSTIC SYMPTOMS

In adults, there was a significant positive correlation between SEB probability and the number of nightly awakenings measured by actigraphy ($\rho = 0.289$, $p = 0.009$). There were no correlations between beta power and sleep maintenance problems. Table 1 shows an overview of the correlations with sleep problems. In addition, a positive correlation was found between awakenings and WM-FP ($\rho = 0.411$, $p = 0.0003$), but not between SEB probability and WM-FP ($\rho = 0.066$, $p = 0.7$); also see figure 2 for a visualization of this triangular relationship. Note, that the latter correlation was performed in a subsample of the "full" sample in which a previous association between SEB probability and impulsivity/WM-FP was found, albeit with a small effect size (and comparable small Spearman's rank correlation coefficient).

Spearman correlations, sleep problems		Frontocentral beta power	SEB probability
Actigraphy, WASO			
	Coefficient	0.051	0.109
	p-value	0.607	0.266
	N	105	105
Actigraphy, awakenings			
	Coefficient	0.072	0.289
	p-value	0.528	0.009
	N	80	80

Table 1. Correlations between sleep problems and EEG parameters.
Effect sizes of Spearman correlations between sleep problems (wake after sleep onset [WASO] and awakenings) measured by actigraphy, and two different EEG parameters (frontocentral beta power and SEB [spindling excessive beta] probability, in adults only. The Bonferroni-significance level is $\alpha = 0.05/4 = 0.0125$.

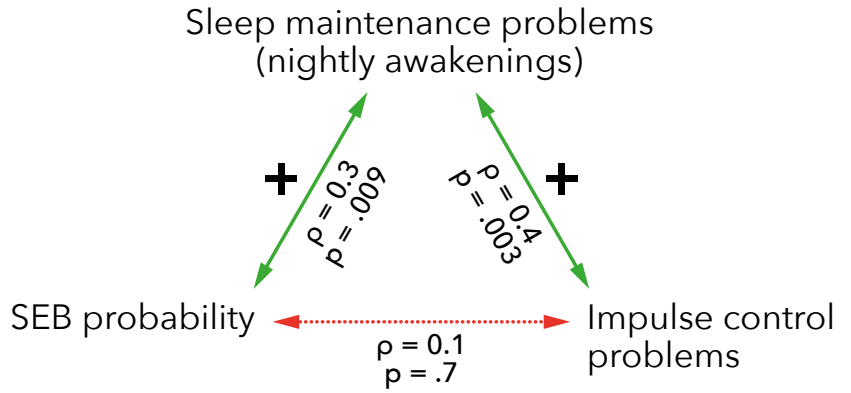


Figure 2. Triangular relationship between sleep problems, SEB probability and impulse control. A significant positive correlation was identified between nightly awakenings and both SEB (spindling excessive beta) probability and impulse control problems. However, no significant correlation was found between SEB probability and impulse control problems, implying that sleep maintenance problems cause both the presence of SEB as well as the impulse control problems.

TRANSLATION PHASE

ADHD DIAGNOSIS

Children with a diagnosis of ADHD had a significantly lower beta power ($F = 19.235$, $p = 0.00001$, Cohen's $d = -0.427$) and higher SEB probability ($F = 46.824$, $p < 0.00001$, $d = 0.744$) compared to healthy children. There was no group x sex interaction for both beta power and SEB probability. See Supplementary Results for an additional discriminant analysis.

Among all children with ADHD, there was also an inverse correlation between beta power and baseline ADHD-RS-IV score ($\rho = -0.149$, $p = 0.007$), and a positive correlation between SEB probability and baseline score ($\rho = 0.147$, $p = 0.008$). Sensitivity analysis showed that correlations with beta power were greater in boys ($\rho = -0.179$, $p = 0.006$) and non-significant in girls.

ADHD REMISSION

With regard to methylphenidate treatment, there was no main effect for beta power on the total ADHD sample, no significant response x sex interaction (p = 0.087), but a difference between girls and boys (p = 0.013). A sensitivity analysis for boys and girls separately (figure 3A), revealed that remitting girls had a significantly higher beta power at baseline compared to non-remitting girls (F = 5.762, p = 0.019, *d* = 0.598), but no significant effect was found in boys. For response, there was a main effect on the total ADHD sample (F = 5.254, p = 0.023, *d* = 0.177), and a significant response x sex interaction (p = 0.020). Repeating the analysis for boys and girls separately revealed that responding girls had a significantly higher beta power (F = 7.677, p = 0.007, *d* = 0.672), while no effect was found in boys. Using the optimal cut-off point determined by maximizing the Youden Index for beta power in girls (0.7530, *J* = 0.308), a PPV of 44% (nPPV = 139%) was reached, with a sensitivity of 75%.

There were no significant main or interaction effects for remission or response observed in the overall ADHD sample concerning SEB probability, only a trend towards an interaction effect for response (p = 0.055). However, in line with the differential findings for boys and girls with ADHD, we found opposite patterns (post-hoc) between boys and girls (figure 3B). Boys who responded to methylphenidate had a higher SEB probability at baseline compared to non-responders (F = 5.706, p = 0.018, *d* = 0.273), while there was no effect for remission. All effects were non-significant in girls.

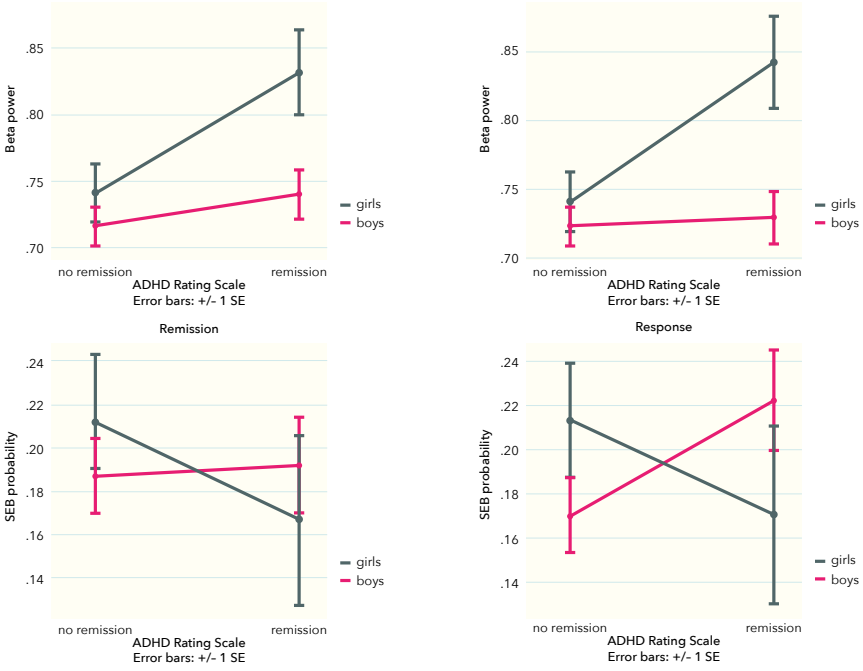


Figure 3. Treatment effects in girls and boys diagnosed with ADHD. Remitting and responding girls have a higher beta power at baseline compared to non-remitting and non-responding girls, while there is no significant difference in boys (A). Opposite sex effects are observed for SEB probability, although statistically significant effects are only found for response in boys only (B).

MDD REMISSION

Medication sample: No significant correlation was found between baseline QIDS and beta power (ρ = 0.001, p = 0.97) or SEB probability (ρ = 0.078, p = 0.052).

For beta power, there was a main effect for remission (F = 5.241, p = 0.022); remitters had a lower beta power at baseline compared to non-remitters (*d* = -0.229). No interaction effect for the type of antidepressant (escitalopram, sertraline or venlafaxine) or sex was found (figure 4A).

In contrast, for SEB probability there was a significant remission x treatment interaction (p = 0.020): remitters to sertraline had a

higher SEB probability (F = 7.379, p = 0.007, *d* = 0.269) compared to non-remitters, while no statistical differences were found for the other two antidepressants (figure 4B). Furthermore, sensitivity analyses revealed that the effects were in the same direction for men and women. Based on the optimal cut-off values of SEB probability for sertraline (0.1034, *J* = 0.185) and beta power for escitalopram and venlafaxine (0.8448, *J* = 0.132), a PPV of 46% (nPPV = 127%) and 44% (nPPV = 113%) were reached respectively. The same results were found when the SEB cut-off was applied to the escitalopram and venlafaxine group.

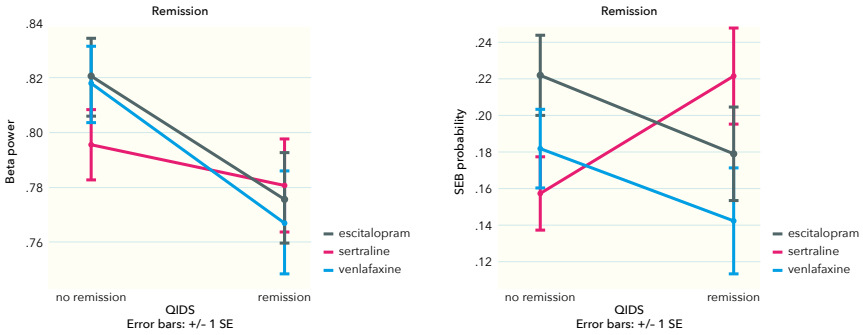


Figure 4. *Treatment effects in adults diagnosed with MDD. Remitting patients have a lower beta power at baseline compared to non-remitting patients, which is more evident in patients treated with escitalopram or venlafaxine (A). Remitters to sertraline have a higher SEB probability at baseline compared to non-remitters, while remitting patients on the other two antidepressants have a lower SEB probability compared to non-remitters (B).*

TMS sample: There was no significant correlation between baseline BDI and beta power (ρ = -0.097, p = 0.18) or SEB probability (ρ = 0.026, p = 0.720). Moreover, we found no treatment response effects.

DISCUSSION

Here, we validate a first transdiagnostic RDoC in the arousal/regulatory domain, where – in line with prior research (Arns, Swatzyna, et al. 2015) – objective sleep maintenance problems (number of awakenings) cause impulse control problems, accompanied by a beta-band EEG signature (frontocentral SEB probability). This beta-band signature is thus reflective of a hypoarousal state, specifically caused by sleep maintenance problems. In the next steps, these beta band signatures were differentially associated with treatment response in ADHD and MDD.

Of the 54 functional networks that were identified through a data-driven data-reduction method, encompassing all major EEG frequency bands (as described in Meijs et al. (Meijs et al. 2024)), specifically a left-frontal beta network was associated with impulse control. This validation was reinforced by the finding that two operationalizations for prefrontal beta activity – 1) frontocentral spectral beta power and 2) an artificial neural network classification of SEB probability, thereby automating the detection of beta spindles – were significantly associated with impulse control in a large dataset (from TDBRAIN+), albeit with small effect sizes, especially for SEB probability. Interestingly, while the discovered functional network, spectral beta power and SEB, all comprise prefrontal beta activity, there were low correlations between all three signatures. This finding suggests these EEG signatures capture different elements of this RDoC construct.

Consistent with the RDoC approach, we used sleep-wake (a dimension within the arousal/regulatory systems domain) for mechanistic validation. Thereby, we replicated previous work that reported an association between sleep maintenance, impulse control and SEB (Arns, Swatzyna, et al. 2015), in a subsample of patients for whom sleep data were available. Here, we used actigraphy as an objective measure for sleep problems and the two different operationalizations as described above, that can be objectively obtained and do not directly depend on visual inspection. In line with prior work, we found positive correlations, with a medium effect size, between nightly

awakenings and poor impulse control as well as the probability of having SEB. However, the previously identified association between impulse control and SEB probability in the large sample (albeit with small effect size and positive correlation), did not reach statistical significance in the smaller sample. These results indicate that the smaller sample was underpowered. They also confirm the directionality, consistent with prior research, implying that sleep is a common factor in such a way that sleep maintenance difficulties cause SEB to occur and also may lead to daytime hypoarousal and poor impulse control, thereby impacting daily functioning. Hence, this EEG signature, that thus indexes hypoarousal and impulse control, may hold significant importance in clinical settings. Patients exhibiting high SEB probability could potentially benefit from integrated sleep management strategies into their treatment plan, such as additional cognitive behavioral therapy for insomnia (CBT-I). This approach holds the potential to improve not only the quality of sleep but also to yield advantages across various cognitive, emotional, and behavioral aspects (Arns, Kooij, and Coogan 2021).

Interestingly, a diagnosis of ADHD was associated with high SEB probability, but low spectral beta power, with a large to medium effect size respectively. Beta power was inversely correlated to ADHD severity, while there was a positive correlation between SEB probability and severity. The latter findings were evident in males, with no statistical significance found in females. While this finding sounds counterintuitive, it might well be that these two operationalizations pick up two qualitatively different subgroups of ADHD: one characterized by overall low beta power (as often seen as elevated theta-beta ratio in patients diagnosed with ADHD, a frequently replicated finding (Barry, Clarke, and Johnstone 2003), although non-replication is also reported (Arns et al. 2018)), and one with SEB, possibly too infrequent to contribute to overall spectral beta power. These results emphasize the complementarity of both metrics. This is especially evident from the differential effects for treatment outcome in girls and boys: higher beta power was associated with remission and response to methylphenidate in girls with ADHD, while higher SEB probability was associated with a better treatment outcome in boys, although results were statistically non-significant. Among girls,

an achieved PPV of 44% may appear low; however, this indicates an improved remission rate (nPPV) of +39%.

For MDD, no associations with symptom severity were found. However, a drug-specific effect was found: low beta power being predictive of remission to all three antidepressants, but the effect was evidently strongest for escitalopram and venlafaxine. On the other hand, high SEB probability was associated with remission to sertraline. Moreover, the presence of SEB seems to be of value for stratification purposes regarding antidepressant treatment: if SEB probability is high, MDD patients are more likely to remit to sertraline, while if it is low, patients are more likely to remit to escitalopram or venlafaxine. Based on the optimal cut-off for SEB probability, PPVs of 46% for sertraline and 44% for the other antidepressants were reached, corresponding to nPPVs of respectively +27% and +13%.
These results match earlier results where patients with EEG abnormalities responded better to sertraline (Arns, Gordon, and Boutros 2017), and normalization of EEG abnormality after eight weeks of treatment being specifically associated with response to sertraline and not escitalopram (Van der Vinne et al. 2019). In the older literature the occurrence of spindles and related oscillations was considered an EEG abnormality related to epileptic activity (Niedermeyer and Silva 1999), which in current neurological practice is not regarded as such. SEB is frequently found in the ADHD population, up to 13-20% (Chabot and Serfontein 1996; Clarke et al. 2001c), and also found in healthy controls (Arns et al. 2008), suggesting SEB is not a neurologic abnormality, but rather an 'instable' state marker that is caused by different factors, such as sleep problems often seen in ADHD patients (Arns and Olbrich 2014; Roumen and Serge 2014), and seen more frequently in patients with epileptiform activity without being of neurologic diagnostic value.

Sertraline, in contrast to the other two antidepressants, is a synaptic dopamine reuptake inhibitor that increases extracellular levels of dopamine (Tatsumia et al. 1997; Kitaichi et al. 2010). The literature supports dysfunction of the dopamine system and the presence of associations with dopamine genes in ADHD (Swanson et al. 2007). Furthermore, downregulation of the dopamine system, leading to

dysfunction of neural circuits such as prefrontal cortex-amygdala functional connectivity, has been implicated in the pathophysiology of MDD (Belujon and Grace 2017). Thus, our findings suggest that the presence of SEB (in particular in combination with low frontocentral beta power) might indicate a disrupted dopamine system leading to ADHD or depressive symptoms, and therefore allows treatment outcome prediction.

Research has found a link between dopamine and the regulation of sleep, reinforcing the potential use of SEB as an indicative marker for sleep problems associated to psychiatric disorders. Dopamine plays a role in sleep regulation by promoting waking (Monti and Jantos 2008), and brain dopamine levels and dopamine transporter (DAT) expression and function show circadian fluctuations (Kesner and Lovinger 2021). Furthermore, genetic variations in DAT have been linked to sleep EEG patterns, such as the presence of slow-way activity (Kenneth et al. 2014). Additionally, polymorphisms in the gene encoding Catechol-O-methyltransferase (COMT), an enzyme involved in the metabolic breakdown of dopamine, are associated to dopaminergic function in the prefrontal cortex, and may affect cognitive function, behavior, sleep architecture, susceptibility to sleep deprivation, the sleep EEG, and responsiveness to stimulant treatment (Dauvilliers, Tafti, and Landolt 2015; Kenneth et al. 2014).

The current study has several strengths, such as the use of multiple large samples. A large heterogeneous dataset that consisted of patients with various psychiatric disorders was included for investigating the relation between impulse control, sleep and EEG beta activity. The datasets for translating the findings for clinical value were all independent of each other. Moreover, we used objective measures for impulse control (measured by false positives on a continuous performance task), sleep maintenance (measured by actigraphy), and EEG features (power calculation, deep learning algorithm and fICA). However, important limitations of the study include the lack of a placebo-controlled arm, and risk of bias and confounding related to the open-label design of the included trials. Furthermore, the opportunity for out-of-sample validation was restricted due to variations in EEG equipment and montages among a potential inde-

pendent ADHD sample. However, given the substantial sample size and consequent high power, we deem our approach to be sufficiently robust (Klooster et al. 2023).

In conclusion, we validated the specificity of frontal beta activity being associated with impulse control, firstly by a fICA on source level that was not limited to the beta band, and secondly using two different operationalizations for frontocentral beta activity (conventional power calculation and training a CNN for classifying SEB). We replicated the triangular relationship involving SEB, sleep and impulse control, positing SEB as a state rather than a trait marker caused by sleep maintenance problems with concurrent poor impulse control. Future research should therefore prioritize investigating sleep problems to enhance our understanding of impulsivity problems. Lastly, we found that frontocentral beta power and SEB probability were differentially associated with medication treatment outcome in boys and girls with ADHD, as well as drug-specifically associated with treatment outcome in adult MDD patients.

SUPPLEMENTARY INFORMATION

SUPPLEMENTARY MATERIALS AND METHODS

DEVELOPMENT OF AN ALGORITHM TO CLASSIFY SEB

A convolutional neural network (CNN) model was trained while that type of model previously has been successfully used for the analysis of EEG in several studies (Tjepkema-Cloostermans, Carvalho, and Putten 2018; Putten, Olbrich, and Arns 2018). For the training of a CNN deep learning model to classify SEB in the EEG, data from 197 subjects (a subset TDBRAIN dataset, diagnosed with ADHD, OCD or insomnia) were used. These datasets were visually annotated by an EEG expert (MA) blinded to diagnostic status, behavioral scores and clinical outcomes, and classified. For this purpose, the EEG data were segmented into two second segments with a sliding window of 0.2 seconds, and downsampled from 500 Hz to 125 Hz. This downsampling meant that each segment could be represented 4 times containing different samples (starting from sample 0, 1, 2 and 3). From participants that showed SEB in some segments, all segments containing no SEB were not used in subsequent analysis. Since only 6.9% of the segments was classified as SEB, this minority class was oversampled replicating segments with SEB to get a balanced class distribution yielding a total of 205,132 segments. Additionally, layers (or channels) were added to the training examples for the model, where electrodes were clustered into left-, central- and right electrodes which were stacked in a different order for each channel, leading to a depth of 7 channels. The CNN model was built and trained using TensorFlow functional Keras API (Abadi et al. 2016) version 2.4.1, and to find the optimal parameters and hyperparameters the hyperband tuner from the KerasTuner package (https://keras.io/keras_tuner, version 1.2.1a) was used (the parameter space is depicted in Table S1). Tuning was done on a random subsample of 75,000 segments. The parameter set selected for training had the lowest sparse categorical crossentropy loss. The model architecture is depicted in figure S1. For training the data was divided in a train set of 80% of the data, a validation set containing 10% of the data and a test set of 10%, using a 10-fold cross-validation, while taking care data of a single subject did not overlap between data partitions (using GroupShuffleSplit from the scikit learn package (Pedregosa et al. 2012)).

(Hyper) parameter	space	
Kernel height	[1, 2, 3]	
Kernel width	[1, 2, 5, 25]	
Number of convolutional blocks	[1, 2, 3]	
	CNN layer: Number of filters	[10, 20, 30, 40, 50, 60]
	Pooling layer:	['max', 'average']
	Dropout:	[0, 0.1, 0.25]
GlobalPooling	['max', 'average']	
Optimizer	['Adamax', 'sgd']	
LearningRate	[4e-3, 1e-2]	

Table S1. (Hyper)parameter search space for Keras Tuner.

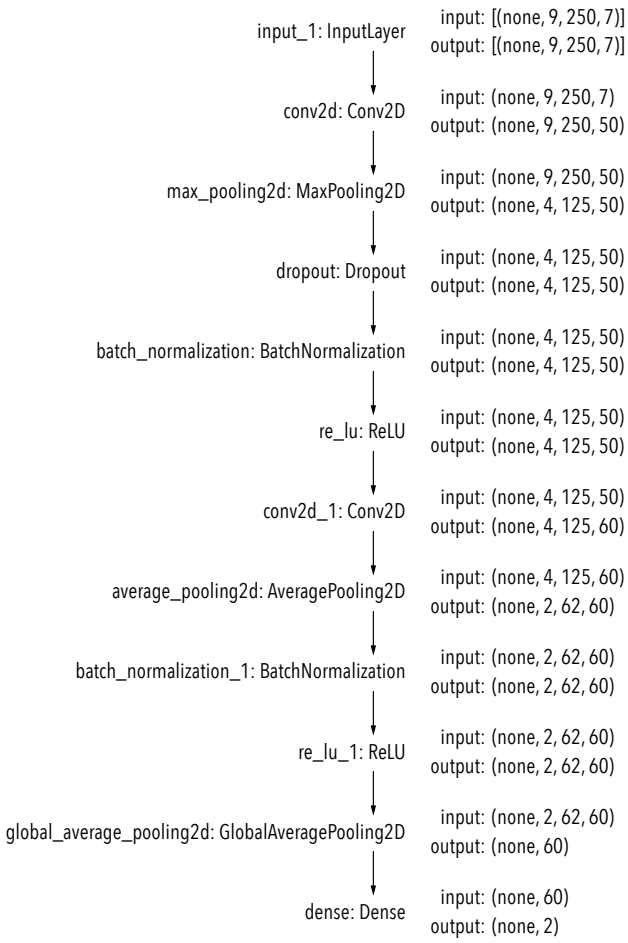


Figure S1. Model architecture.

SUPPLEMENTARY RESULTS

ADHD DIAGNOSIS

Discriminant analysis revealed that a prediction model of both predictors performed better (Wilk's Lambda, $\lambda = 0.864$; Chi-Square, $\chi^2 = 69.760$; $p < 0.00001$) than beta power ($\lambda = 0.960$; $\chi^2 = 19.561$; $p = 0.00001$) or SEB ($\lambda = 0.910$; $\chi^2 = 44.821$; $p < 0.00001$) alone. Optimal thresholds for beta power and SEB probability were established based on the maximum Youden Index. According to these cut-offs, ADHD diagnosis occurred in 83% of children exhibiting a high SEB probability and 87% of those displaying both low beta power and high SEB probability. Specificity for SEB probability was 76%, but sensitivity was modest at 56%.

Cross-tabulations were constructed using the optimal cut-off points for diagnosing ADHD, remission to methylphenidate in girls with ADHD, and remission to antidepressant medication in MDD. The results of these cross-tabulations are shown in figure S2.

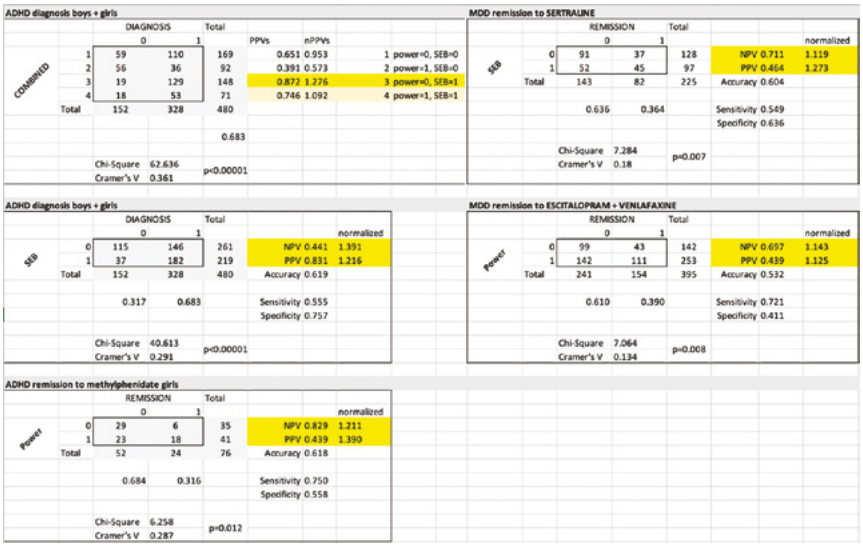


Figure S2. Cross-tabulations were generated using optimal cut-off values for remission, determined by the maximum Youden Index for SEB probability ("SEB"), beta power ("Power") or both metrics combined; 0 = non-remission; 1 = remission. The negative and positive predictive value (NPV and PPV; also normalized for the actual remission rate), and both sensitivity and specificity, were calculated. Columns represent the actual (non-)remission rates, rows the (non-)remission rates based on the cut-offs.

5

GENERAL DISCUSSION

THESIS OVERVIEW

In this thesis, the central focus was the shift from traditional psychiatric care –which relies on symptom clusters for diagnosis and a 'diagnosis-informed one-size-fits-all' approach for treatment decisions, leading to varied treatment outcome and imprecise interventions– towards a stratified psychiatry approach grounded in a transdiagnostic framework. Therefore, we aimed to identify transdiagnostic markers for predicting treatment response in psychiatric disorders. Using a novel, transdiagnostic approach, we leveraged large and heterogeneous datasets of psychiatric patients (comprising a total of over 5,000 EEGs) to capture a diverse range of EEG features potentially predictive of treatment outcome. The eLORETA-fICA method, utilized in this thesis as a data-driven data-reduction technique, yielded independent EEG components, or functional brain networks (data-reduction), by identifying data-driven patterns within the EEG data, thereby preserving all information. We utilized independent datasets (comprising a total of over 1,500 EEGs), encompassing adult patients with major depressive disorder (MDD) and children diagnosed with attention deficit and hyperactivity disorder (ADHD), for treatment prediction purposes.

GENETICS AS GROUND TRUTH: POLYGENIC ASSOCIATION ANALYSIS

Considering that existing classification systems exhibit inconsistent predictability regarding treatment outcome (Insel et al. 2010; Morris and Cuthbert 2012), and that the alignment between neurobiology on the one hand and (subjective) psychological measures (and amongst) on the other hand is limited (Krepel et al. 2019; Van der Vinne et al. 2017; Saveanu et al. 2015), we embraced a genetic-informed strategy to first find biologically plausible functional networks (figure 1). The networks derived from eLORETA-fICA were associated to polygenic scores of antidepressant response (PGS-AR), representing the genetic susceptibility of individuals to respond to antidepressant treatment in this context. Polygenic (risk) scores are biologically grounded, objective measurements based on genetic data, making them less susceptible to bias or interpretation influenced by individual perspectives (Lewis and Vassos 2020; Wray et al. 2021).

Nonetheless, polygenic scores alone are unlikely to conclusively predict future diagnoses or treatment outcomes, as they can only capture a portion of the genetic influences, which, in turn, account for only a fraction of the overall risk (Wray et al. 2021). They can, however, be used for stratification purposes. By employing polygenic association analysis, as we did in the first two studies (chapter 2 and 3), the likelihood of discovering a biologically meaningful functional network capable of predicting differential treatment response is increased. The main results indicate that our innovative approach, using PGS-AR association analysis as an intermediate step to select networks obtained through eLORETA-fICA, can successfully identify functional networks with sex-specific and medication-specific treatment predictive capabilities for MDD.

OPERATIONALIZATIONS FOR FRONTAL BETA ACTIVITY

In the last study (chapter 4), we chose not to integrate the genetics-informed approach. Instead, emphasis was placed on the intersection between biology and psychology, using objective measures for impulse control (false positives errors or errors of commission on a continuous performance task) as well as for objective sleep-wake measures using actigraphy. We investigated how these neuropsy-

chological measures were related to two operationalizations for EEG beta activity in frontocentral brain regions, within the RDoC arousal/regulatory domain: 1) beta power and 2) spindling excessive beta (SEB) probability, a measure that we derived through deep learning. The implementation of a deep learning algorithm for automatically identifying SEB enabled us to conduct this large-scale study, overcoming the limitations of the previous reliance on labor-intensive and subjective visual inspection.

Here, the eLORETA-fICA method was employed to confirm the presence of frontal beta activity associated with impulse control. These results replicate a prior study (Arns, Swatzyna, et al. 2015), supporting the concept that SEB is not directly, but rather indirectly (mediated by sleep problems) related to impulse control. We concluded that our findings indicate that SEB is a transdiagnostic state marker for hypoarousal caused by sleep maintenance problems. Notably, poor sleep maintenance was linked to poor impulse control. This link that has been contextualized within a more comprehensive understanding of the intricate interplay among regulatory mechanisms governing sleep, arousal, affect, and attention within the overarching circuitry of arousal regulation (Dahl 1996). Lastly, we discovered that both operationalizations of beta activity exhibit sex-specific and medication-specific predictive potential for treatments in both ADHD and MDD.

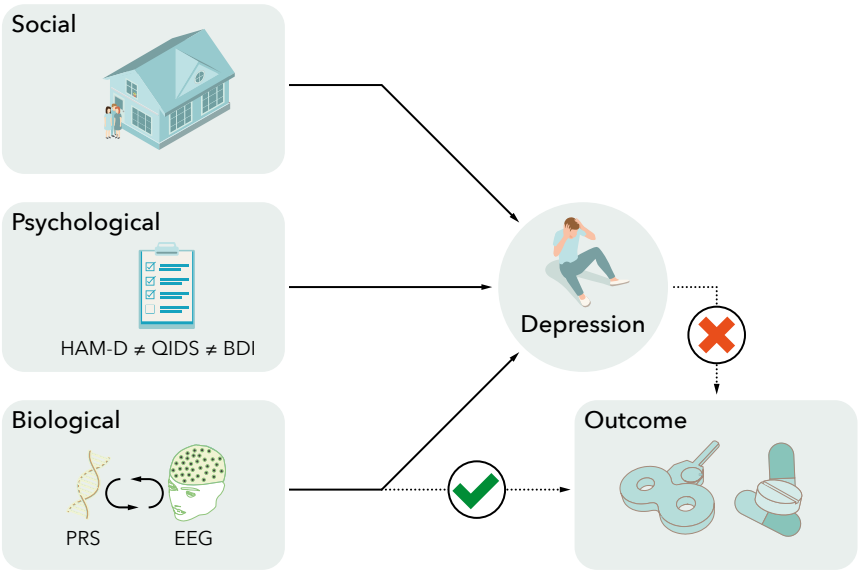


Figure 1. *Adhering to the biopsychosocial model, depression arises from a combination of biological, psychological, and social factors. Diagnosis relies on clinical symptom observation, often supplemented by subjective questionnaires. However, these questionnaires may not consistently align with each other or with current classification systems, which may not fully capture underlying mechanisms of depression. Due to the lack of reliable predictors for treatment success, a stepped care approach is common. Consequently, our objective was to identify biologically plausible brain networks capable of predicting treatment outcomes. We employed an intermediate step approach associating these networks with polygenic scores, thus circumventing subjective measures by integrating two objective measures.*

FUNCTIONAL NETWORKS

The EEG components obtained with eLORETA-fICA are computationally derived, statistically independent networks that do not necessarily reflect existing networks (figure 2). However, our primary aim was not to find or investigate existing brain networks, nor to discover depression-specific networks, but rather to explore diagnosis-independent, universal brain networks, following the Research Domain Criteria (RDoC) approach. Consequently, we derived networks from a heterogeneous sample to predict treatment outcomes in MDD and ADHD, emphasizing a universal and transdiagnostic,

rather than a diagnosis-specific focus. Additionally, in prior work (Voetterl et al. 2022), EEG biomarkers were developed on both TD-BRAIN+ (Two Decades-Brainclinics Research Archive for Insights in Neurophysiology, plus data from other clinics) and large groups of healthy controls. The results revealed that biomarkers developed on TDBRAIN+ generalized well to healthy controls, while the model developed on healthy controls did not generalize well to TDBRAIN+. Consequently, we prioritized the development of networks on the largest dataset available (TDBRAIN+). This approach presents both a strength, allowing for maximal variance, and a potential limitation due to its non-specific nature. Future research should delve into the broader implications of eLORETA-fICA networks for other disorders or transdiagnostic purposes.

SLOW WAVE NETWORK

In our proof-of-concept study (chapter 2), utilizing the eLORETA-fICA method, we derived 29 functional networks from a large heterogenous sample (N = 1,195). The network significantly associated with PGS-AR proved challenging to interpret, as it was characterized by slow wave activity in multiple, anti-correlated brain areas. This scatteredness observed, a phenomenon we found in all networks, may be attributed to the use of high-density EEG (65 channels). Intriguingly, the association with PGS-AR was only discerned in men, and the slow wave network emerged as a male-specific predictor of response. This alignment substantiates the utility of a polygenic-informed approach.

POSTERIOR ALPHA NETWORK

In the follow-up study (chapter 3), eLORETA-fICA was applied to a nearly four times larger, heterogenous cohort of psychiatric patients including the full lifespan (N = 4,045), albeit with a lower density of EEG channels (26 channels). This analysis captured a broader range of diagnosis-independent neurobiological EEG features, resulting in 54 functional networks. Again, we carried out an PGS-AR association analysis, but in an independent sample: the cohort initially employed for eLORETA-fICA in the first study. Thus, we followed a two-step

process for the discovery of the network (in contrast to the proof-of-concept study): development in the first dataset and validation in the second. An age-related posterior alpha network that explained >60% of the EEG variance was identified. The posterior alpha network reflected alpha oscillations in the parietal lobe, which were inversely related to alpha oscillations in the occipital lobe. It is known that posterior alpha waves occur primarily during relaxed wakefulness, and can be best seen with eyes closed (Klimesch 1999).

Given the network's strong association with age and visual resemblance to EEG vigilance stages, it was anticipated that children, the elderly, or adults with less sleep might exhibit a distinct pattern of network activity over the course of EEG recordings, reflecting quicker transitions into lower EEG arousal/vigilance stages. Moreover, there is evidence that MDD patients exhibit fewer and delayed declines into lower EEG-vigilance stages compared to healthy controls, marked by increased alpha activity and decreased non-alpha EEG (Hegerl et al. 2011; Ulke et al. 2018). However, no correlation was observed between age, sleep duration, or other baseline variables and the changes in network activity over time. Additionally, the network displayed remarkable stability across recording intervals, as evidenced by a very high intraclass correlation coefficient (ICC = 0.98). This stability, coupled with its genetic associations, suggests that the posterior alpha network represents a trait rather than a transient state feature, which is supported by prior research that found that resting state alpha is a stable trait characteristic (Tenke et al. 2018; Allen et al. 2004; Smit et al. 2005). However, our discovery of a relation with age suggests a potential neurodevelopmental aspect to the network. Physiological aging involves a power increase of the occipital alpha rhythms during childhood, followed by a power decrease in adulthood, with changes occurring faster in posterior regions than in frontal regions (Clarke et al. 2001a; Chiang et al. 2011; Babiloni et al. 2006), aligning closely with our study's observations. Thus, the network could serve as a neurodevelopmental trait marker with predictive significance for both lifetime depression and treatment outcomes.

FRONTAL BETA NETWORK

In the final study (chapter 4), instead of conducting another eLORETA-fICA, we employed the 54 functional networks obtained in the abovementioned follow-up study for further analyses. This time, in contrast to the prior approach with PGS-AR, we utilized a dichotomous measure for impulse control, established through the number false positive errors (0 or >1) on a working memory task. We found that patients with poor impulse control exhibited heightened activity in a frontal beta network. This network primarily showed (left-sided) beta activity at the prefrontal cortex (PFC) and a small anticorrelated beta component at the (left) primary somatosensory cortex that is not fully comprehended, thereby providing independent confirmation of our hypothesis linking frontal beta activity to impulse control. Emerging evidence supports the involvement of the PFC in the arousal circuitry (Mashour, Pal, and Brown 2022), including an important role in controlling impulsivity (Kim and Lee 2011).

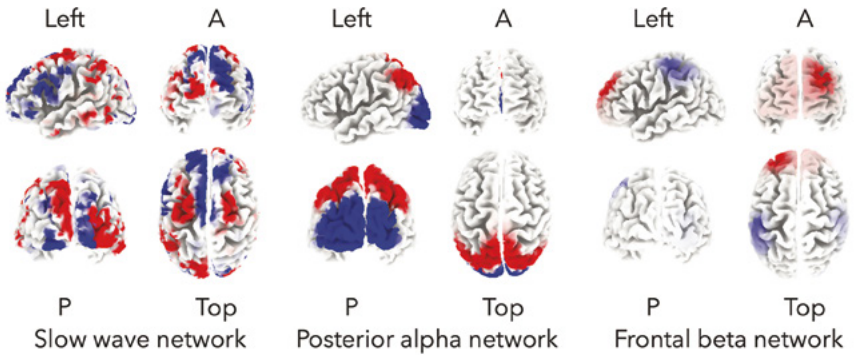


Figure 2. The three functional networks identified in this thesis, visualized from four different angles. The two colors represent joint neural activation and deactivation (anticorrelation). The network's neural oscillation frequency varies, encompassing mainly slow delta and some theta oscillations (left: slow wave network), alpha oscillations (middle: posterior alpha network), and beta oscillations (right: frontal beta network). All networks were derived by eLORERA-fICA using two independent large heterogenous cohorts (the slow wave network: N = 1,123; the posterior alpha network and frontal network: TDBRAIN+, N = 4,045). A = anterior, P = posterior.

CLINICAL RELEVANCE

The findings of this thesis underscore the potential of functional networks as prognostic indicators in clinical settings. Individual functional network scores can be easily and cost-effectively derived from resting-state EEG recordings, requiring a minimum of 19 channels but remaining independent of the EEG apparatus used. Based on these network scores, patients with MDD can be stratified to the most appropriate antidepressant treatment with the highest likelihood of achieving remission before the initiation of treatment.

THE NETWORK-BASED STRATEGY

In our proof-of-concept study, the slow wave network emerged as a sex-specific, non-treatment-specific, and unidirectional predictor for antidepressant response. Thus, although the normalized positive predictive value (PPV) indicated a predicted increase in response rate of about 25% for all treatments, the network showed no stratification potential, which is desired for clinical purposes. However, in the follow-up study, the discovered posterior-alpha ageing network was significantly associated with remission to two different evidence-based treatments for MDD, in a drug-class specific (only venlafaxine) and sex-specific (opposite directions for TMS and concurrent psychotherapy in men and women) manner. Thus, this network demonstrated stratification potential. The normalized PPV indicated an improvement of the remission rate of more than 30% in both male and female patients with MDD.

THE RDOC APPROACH

In the last study, the deep learning derived SEB probability demonstrated potential for antidepressant medication stratification in MDD patients, effectively guiding treatment choices towards three different antidepressants. Notably, the normalized PPV for remission of this stratification indicated an increased remission rate of 27% for sertraline and 13% for escitalopram and venlafaxine. Within this cohort, frontocentral beta power emerged as an unprecedented treat-

ment predictor exclusive to girls with ADHD, increased beta power being associated with better response to methylphenidate, showcasing a nearly 40% increase in remission rates. This finding stands in contrast to all other predictors for ADHD treatment outcome, which were found to be applicable to boys only.

REVOLUTIONIZING TREATMENT PARADIGMS

In conclusion, the innovative network-based strategy and RDoC approach are poised to become pivotal tools in future treatment paradigms, contributing to the development of stratified and, later perhaps, personalized medicine. Those strategies provide a more targeted and efficient alternative to the current stepped-care, 'trial-and-error' practice.

TREATMENT AND SEX-SPECIFIC EFFECTS

We observed effects that were specific to both sex and treatment. The slow wave network predicted responses to all treatment modalities but only in males. In contrast, the posterior alpha network served as a drug-specific predictor, and differentially predicted remission to TMS and concurrent psychotherapy for men and women. Additionally, the frontal beta network was consistently associated with impulsivity in both sexes, indicating poorer impulse control was related to elevated frontal beta activity. However, both operationalizations for frontocentral beta activity –beta power and SEB probability– were differentially predictive of the outcome of psychopharmacotherapy, specifically for girls and the type of antidepressant, respectively.

DIFFERENCES BETWEEN ANTIDEPRESSANT PSYCHOPHARMACOTHERAPIES

The slow wave network proved to be a general predictor of antidepressant treatment response in males, whereas the posterior alpha network showed a specific association only with venlafaxine response, not with escitalopram or sertraline. Furthermore, frontocentral SEB probability displayed differential associations with remission, high SEB probability being associated to sertraline remission on one hand, and low SEB probability to escitalopram or venlafaxine remission on the other.

Venlafaxine versus escitalopram and sertraline

Venlafaxine differs from escitalopram and sertraline, which selectively inhibit the reuptake of serotonin (SSRI), primarily because it inhibits the reuptake of both serotonin and norepinephrine (SNRI) in the brain, in a sequential manner (Sansone and Sansone 2014). There is evidence that variations in (the topographical distribution of) alpha activity in MDD distinguish between responders and non-responders to pharmacotherapy in a drug-specific manner. Relatively greater right frontal alpha in women has been associated with a favorable response to escitalopram and sertraline, but not venlafaxine (Arns et al. 2016). Furthermore, increased posterior alpha in MDD has been associated with a better treatment response to antidepressant medications, without showing discernible difference in predictive value for response to SSRI monotherapy versus dual treatment targeting serotonergic and

other monoamine neurotransmitters (Ulrich, Renfordt, and Frick 1986; Bruder et al. 2008; Tenke et al. 2011).

Variations in central nervous system (CNS) and autonomic nervous system arousal profiles could potentially distinguish between outcomes of SSRI and SNRI treatments. A prior study showed that responders and remitters to an SSRI showed a faster decline of CNS-arousal compared to non-responders or non-remitters at baseline, while this pattern did not hold for venlafaxine (Olbrich et al. 2016). This indicates that variations in CNS arousal are not predictive of outcomes with venlafaxine/SNRI treatments, but rather are linked to response with SSRIs. This finding is consistent with our results regarding the stability of the posterior alpha network, which displayed a high level of stability over recording time. This suggests the network does not reflect CNS arousal state. However, this reinforces the conclusion that the posterior alpha network does not predict SSRI response and that its predictive power for venlafaxine response can be attributed to other factors.

Considering that the posterior alpha network specifically predicted response to venlafaxine, this network may reflect noradrenergic projections to the posterior cortex, which could explain its ability to differentiate outcomes between different pharmacologic profiles (SSRI versus SNRI). In other words, the network's activity might be influenced by the noradrenergic effects of venlafaxine, leading to its predictive value in treatment response in a drug-specific manner.

Sertraline versus escitalopram and venlafaxine

Sertraline stands apart from the other two antidepressants due to its modest activity as an inhibitor of dopamine reuptake, which may lead to a distinct pharmacodynamic profile (Sanchez, Reines, and Montgomery 2014; Cipriani et al. 2010). EEG abnormalities, such as paroxysmal activity, observed in depressed patients (without a concurrent neurological condition like epilepsy), have been associated to less favorable treatment outcomes with escitalopram or venlafaxine. However, this association was not observed with sertraline (Arns, Gordon, and Boutros 2017). Moreover, while there were no significant differences in EEG normalization patterns between all three antidepressants, among patients achieving EEG normalization following treatment, it was most

probable to observe a favorable response with sertraline (Van der Vinne et al. 2019). This suggests that sertraline may possess some anticonvulsant properties.

Another explanation lies in its most pronounced inhibitory activity on the dopamine active transporter. Several studies suggest that dopamine plays a role in regulating sleep-wake cycles and arousal, with dopamine promoting arousal and wakefulness (Wisor et al. 2001; Eban-Rothschild et al. 2016; Kaźmierczak and Nicola 2022). Given our discovery of a positive correlation between SEB probability and sleep maintenance problems, as well as the association of high SEB probability with successful remission with sertraline and low SEB probability with remission to other the antidepressants, it is plausible to consider SEB probability as a marker for hypoarousal that delineates depression into two distinct subtypes. One subtype, characterized by hypoarousal, demonstrates a favorable outcome to sertraline due to its dopamine-related effects, while the other, non-hypoaroused subtype, exhibits better outcomes to alternative antidepressants. The finding that high SEB probability was associated with a diagnosis of ADHD, further supports a link between this marker and dopamine. Although questioned, the involvement of dopamine in the etiology of ADHD is based on the facts that dopamine reuptake blockers can reduce ADHD symptoms, and that some patients with ADHD have polymorphisms of genes coding for dopamine regulation, such as dopamine receptor genes (Blum et al. 2008; Swanson et al. 2007). Moreover, evidence indicates a link between dopamine and beta activity, as drugs modulating dopamine and its receptors can effectively influence beta activity levels (Jenkinson and Brown 2011). Additionally, dopamine replacement therapy in parkinsonian patients results in significant increases in alpha and beta power (Melgari et al. 2014). These findings collectively emphasize a relation between (hypo) arousal, dopamine, and beta activity. Deficits in dopamine (regulation) may contribute to hypoarousal, leading to reduced beta power alongside excessive beta spindling.

UNDERSTANDING SEX SPECIFIC EFFECTS

Several recent studies have revealed that deep learning algorithms can accurately discern sex based on EEG data (Putten, Olbrich, and Arns 2018; Bučková et al. 2020; Jochmann et al. 2023). This suggests that sex may act as a confounding factor in EEG analysis, particularly in psychiatric disorders where prevalence differs between sexes. Additionally, a meta-analysis on EEG frontal alpha asymmetry indicated that both sex and age could potentially confound results (Van der Vinne et al. 2017). Consequently, we took these potential confounders into account in our analyses. However, we still found sex-specific effects. Previous research has identified sex-specific predictors of treatment outcome.

Major Depressive Disorder (MDD)

Alpha asymmetry in patients with MDD has been found to be associated with different antidepressant medications in a sex-specific manner, even after controlling for potential confounders such as sex and age (Arns et al. 2016). Furthermore, a recent study employing a novel deep learning pipeline to classify patients' response to TMS found that TMS affects depression differently based on sex (Adamson et al. 2022). Hence, it is plausible that factors associated with sex exert an influence on treatment outcomes. Different biological patterns for women and men with MDD are identified, including variations in markers of the monoaminergic system, immune system, neuroplasticity, as well as certain hormones and neurotransmitters (Labaka et al. 2018). Moreover, several biological factors potentially influence the effectiveness of TMS treatment in women (Hanlon and McCalley 2022): the closer proximity of the brain to the scalp at the PFC (resulting in larger TMS-induced electric fields), the higher density of gray matter and gyrification in the PFC, and elevated levels of estradiol (enhancing cortical excitability). These variations may help explain differences in the prevalence of MDD and responses to TMS treatment observed between male and female MDD patients in our results. Our discovered networks may have captured variations in these biological factors, which could influence the effectiveness of certain MDD treatments differently in women compared to men, thus contributing to the differential treatment prediction.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Sex differences in ADHD have been a topic of ongoing research and debate. Some researchers argue that, while prevalence rates are higher among boys than girls, symptom presentation across sexes tends to be similar (Rucklidge 2010; Cortese et al. 2016). Conversely, other studies contend that girls are often underdiagnosed due to the subtle nature of their symptoms (less prominent hyperactivity and impulsivity, among others), which can have lasting negative impacts on their well-being into adulthood (Quinn and Madhoo 2014; Attoe and Climie 2023). This underscores the pressing need for a biomarker to facilitate ADHD diagnosis in girls. The notion that boys may exhibit more pronounced impulsivity than girls with ADHD is supported by the results of continuous performance tests (Hasson and Fine 2012). Moreover, significant EEG sex-differences in absolute and relative power and theta/beta ratio, including dissimilarities between ADHD subtypes, have been observed between males and females both with and without ADHD (Dupuy et al. 2013; 2021). These results indicate that ADHD influences EEG patterns differently across sexes.

We found no differences between inattention and hyperactivity/impulsivity subscales between boys and girls with ADHD, and identified no sex-specific predictor for diagnosis. Low beta power and high SEB probability in frontocentral regions were found to be associated with ADHD in both sexes, also linked to the severity of symptoms. SEB probability emerged as the strongest association, with 83% of all children exhibiting high SEB probability being diagnosed with ADHD. This indicates that this EEG signature may serve as a potential marker for ADHD regardless of sex.

As regards treatment response, we did identify frontocentral beta power as a sex-specific predictor for remission. It is proposed that stimulant medication has the potential to improve the EEG substrate linked to processing deficits in children diagnosed with ADHD (Clarke et al. 2002; 2003; 2007). Specifically, medication may reduce increased or excessive beta activity in frontal regions, but has also been associated with an increase in reduced frontal relative beta power in girls. Building upon the insights from previous research, it appears plausible that sex-specific EEG patterns are linked to ADHD,

suggesting that methylphenidate may exert distinct effects on these EEG substrates in girls and boys.

FUTURE RESEARCH

In future studies, it is recommended to utilize our proposed 'ground truth scenario', which involves employing various objective measures to uncover biologically plausible transdiagnostic markers for assessing their ability to predict treatment outcomes across a range of psychiatric disorders. Firstly, research could incorporate different polygenic (risk) scores, such as those for schizophrenia (PRS-SCZ) and epilepsy. Recent research has revealed a significant association between PRS-SCZ and electroconvulsive therapy outcomes, which supports the relevance of using PRSs in precision psychiatry (Luykx et al. 2022). Building upon these findings, and upon prior studies that found a link between (epileptiform) EEG abnormalities and drug-specific treatment response (Arns, Gordon, and Boutros 2017; Van der Vinne et al. 2019), associations with PRS for epilepsy may reveal valuable markers able to predict antidepressant or anticonvulsant treatment response in depression, bipolar disorder or other psychiatric disorders.
Furthermore, researchers should concentrate on examining other objective sleep measures and their associations with functional networks. This might extend to understanding how these networks are implicated in (sleep problems associated to) psychiatric disorders and may influence treatment outcomes. Moreover, these studies should investigate the role of sleep disturbances in weakening impulse control and whether addressing these sleep problems (by means of cognitive behavior therapy for insomnia for example) could lead to improvements not only in impulse control but also in other psychiatric symptoms.

Overall, the overarching goal would be to leverage objective measures and advanced analytical techniques to gain deeper insights into the mechanisms underlying treatment response in psychiatric disorders and to develop more personalized and effective treatment strategies.

CONCLUSION

In conclusion, this doctoral thesis represents a step forward in the quest for transdiagnostic markers of treatment response in psychiatric disorders. By leveraging large, heterogenous datasets and integrating objective measures from EEG, genetics, and neuropsychology, we have identified transdiagnostic EEG markers with treatment prediction capabilities. Our findings have highlighted sex-specific and medication-specific effects, which underscores the potential of these markers for stratification approaches that may target specific biological mechanisms underlying psychiatric symptoms, and for developing more personalized and effective treatment strategies. Moving forward, further research and validation are crucial to realizing their full clinical utility and ultimately revolutionizing psychiatric care.

REFERENCES

Abadi, Martín, Ashish Agarwal, Paul Barham, Eugene Brevdo, Zhifeng Chen, Craig Citro, Greg S. Corrado, et al. 2016. "TensorFlow: Large-Scale Machine Learning on Heterogeneous Distributed Systems." *ArXiv*. https://doi.org/10.48550/arxiv.1603.04467.

Adamson, M., A. L. Hadipour, C. Uyulan, T. Erguzel, O. Cerezci, R. Kazemi, A. Phillips, S. Seenivasan, S. Shah, and N. Tarhan. 2022. "Sex Differences in rTMS Treatment Response: A Deep Learning-based EEG Investigation." *Brain and Behavior*, e2696. https://doi.org/10.1002/brb3.2696.

Allen, John J. B., Heather L. Urry, Sabrina K. Hitt, and James A. Coan. 2004. "The Stability of Resting Frontal Electroencephalographic Asymmetry in Depression." *Psychophysiology* 41 (2): 269–80. https://doi.org/10.1111/j.1469-8986.2003.00149.x.

Amare, Azmeraw T., Klaus Oliver Schubert, and Bernhard T. Baune. 2017. "Pharmacogenomics in the Treatment of Mood Disorders: Strategies and Opportunities for Personalized Psychiatry." *EPMA Journal* 8 (3): 211–27. https://doi.org/10.1007/s13167-017-0112-8.

American Psychiatric Association (APA). 2013. "Diagnostic and Statistical Manual of Mental Disorders, *DSM*-5." https://doi.org/10.1176/appi.books.9780890425596.

Aoki, Yasunori, Ryouhei Ishii, Roberto D. Pascual-Marqui, Leonides Canuet, Shunichiro Ikeda, Masahiro Hata, Kaoru Imajo, et al. 2015. "Detection of EEG-Resting State Independent Networks by eLORETA-ICA Method." *Frontiers in Human Neuroscience* 9: 31. https://doi.org/10.3389/fnhum.2015.00031.

Aoun, Mohamed Abo, Benjamin P. Meek, Luc Clair, Sara Wikstrom, Benjamin Prasad, and Mandana Modirrousta. 2022. "Prognostic Factors in Major Depressive Disorder: Comparing Responders and Non-responders to Repetitive Transcranial Magnetic Stimulation (rTMS), a Naturalistic Retrospective Chart Review." *Psychia try and Clinical Neurosciences.* https://doi.org/10.1111/pcn.13488.

Arns, Martijn, Alexander Cerquera, Rafael M. Gutiérrez, Fred Hasselman, and Jan A. Freund. 2014. "Non-Linear EEG Analyses Predict Non-Response to rTMS Treatment in Major Depressive Disorder." *Clinical Neurophysiology* 125 (7): 1392–99. https://doi.org/10.1016/j.clinph.2013.11.022.

Arns, Martijn, Amit Etkin, Ulrich Hegerl, Leanne M. Williams, Charles DeBattista, Donna M. Palmer, Paul B. Fitzgerald, Anthony Harris, Roger deBeuss, and Evian Gordon. 2015. "Frontal and Rostral Anterior Cingulate (rACC) Theta EEG in

Depression: Implications for Treatment Outcome?" *European Neuropsychopharmacology*, , 25 (8): 1190–1200. https://doi.org/10.1016/j.euroneuro.2015.03.007.
Arns, Martijn, and Sebastian Olbrich. 2014. "Personalized Medicine in ADHD and Depression: Use of Pharmaco-EEG." *Current Topics in Behavioral Neurosciences* 21: 345–70. https://doi.org/10.1007/7854_2014_295.
Arns, Martijn, Evian Gordon, and Nash N. Boutros. 2017. "EEG Abnormalities Are Associated With Poorer Depressive Symptom Outcomes With Escitalopram and Venlafaxine-XR, but Not Sertraline: Results From the Multicenter Randomized iSPOT-D Study." *Clinical EEG and Neuroscience* 48 (1): 33–40. https://doi.org/10.1177/1550059415621435.
Arns, Martijn, Gerard Bruder, Ulrich Hegerl, Chris Spooner, Donna M. Palmer, Amit Etkin, Kamran Fallahpour, Justine M Gatt, Laurence Hirshberg, and Evian Gordon. 2016. "EEG Alpha Asymmetry as a Gender-Specific Predictor of Outcome to Acute Treatment with Different Antidepressant Medications in the Randomized iSPOT-D Study." *Clinical Neurophysiology* 127 (1): 509–19. https://doi.org/10.1016/j.clinph.2015.05.032.
Arns, Martijn, Hanneke van Dijk, Jurjen J. Luykx, Guido van Wingen, and Sebastian Olbrich. 2022. "Stratified Psychiatry: Tomorrow's Precision Psychiatry?" *European Neuropsychopharmacology* 55: 14–19. https://doi.org/10.1016/j.euroneuro.2021.10.863.
Arns, Martijn, J.J. Sandra Kooij, and Andrew N. Coogan. 2021. "Review: Identification and Management of Circadian Rhythm Sleep Disorders as a Transdiagnostic Feature in Child and Adolescent Psychiatry." *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2020.12.035.
Arns, Martijn, Jay Gunkelman, Marinus Breteler, and Desiree Spronk. 2008. "EEG Phenotypes Predict Treatment Outcome to Stimulants in Children with ADHD." *Journal of Integrative Neuroscience* 07 (03): 421–38. https://doi.org/10.1142/s0219635208001897.
Arns, Martijn, Jay Gunkelman, Sebastian Olbrich, Christian Sander, and Ulrich Hegerl. 2011. "Vigilance and Phenotypes in Neuropsychiatry: Implications for Intervention." In *Neurofeedback and Neuromodulation Techniques and Applications*, edited by Coben R., Evans J. R., 79-123. Academic Press. https://doi.org/10.1016/b978-0-12-382235-2.00004-4.
Arns, Martijn, Madelon A. Vollebregt, Donna Palmer, Chris Spooner, Evian Gordon, Michael Kohn, Simon Clarke, Glen R. Elliott, and Jan K. Buitelaar. 2018. "Electroencephalographic Biomarkers as Predictors of Methylphenidate Response in Attention-Deficit/Hyperactivity Disorder." *European Neuropsychopharmacology*, 28 (8): 881–91. https://doi.org/10.1016/j.euroneuro.2018.06.002.
Arns, Martijn, Ron J. Swatzyna, Jay Gunkelman, and Sebastian Olbrich. 2015. "Sleep Maintenance, Spindling Excessive Beta and Impulse Control: An RDoC Arousal and Regulatory Systems Approach?" *Neuropsychiatric Electrophysiology* 1 (1): 5. https://doi.org/10.1186/s40810-015-0005-9.
Arns, Martijn, Sebastian Olbrich, and Alexander T. Sack. 2023. "Biomarker-Driven Stratified Psychiatry: From Stepped-Care to Matched-Care in Mental Health." *Nature Mental Health*, 1–3. https://doi.org/10.1038/s44220-023-00156-3.
Attoe, Darby E., and Emma A. Climie. 2023. "Miss. Diagnosis: A Systematic Review of ADHD in Adult Women." *Journal of Attention Disorders* 27 (7): 645–57. https://doi.org/10.1177/10870547231161533.
Babiloni, Claudio, Giuliano Binetti, Andrea Cassarino, Gloria Dal Forno, Claudio Del

Percio, Florinda Ferreri, Raffaele Ferri, et al. 2006. "Sources of Cortical Rhythms in Adults during Physiological Aging: A Multicentric EEG Study." *Human Brain Mapping* 27 (2): 162–72. https://doi.org/10.1002/hbm.20175.

Bagby, R. Michael, Andrew G. Ryder, Deborah R. Schuller, and Margarita B. Marshall. 2004. "The Hamilton Depression Rating Scale: Has the Gold Standard Become a Lead Weight?" *American Journal of Psychiatry* 161 (12): 2163–77. https://doi.org/10.1176/appi.ajp.161.12.2163.

Barlow, David H., Todd J. Farchione, Jacqueline R. Bullis, Matthew W. Gallagher, Heather Murray-Latin, Shannon Sauer-Zavala, Kate H. Bentley, et al. 2017. "The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders Compared With Diagnosis-Specific Protocols for Anxiety Disorders: A Randomized Clinical Trial." *JAMA Psychiatry* 74 (9): 875. https://doi.org/10.1001/jamapsychiatry.2017.2164.

Barry, Robert J., Adam R. Clarke, and Stuart J. Johnstone. 2003. "A Review of Electrophysiology in Attention-Deficit/Hyperactivity Disorder: I. Qualitative and Quantitative Electroencephalography." *Clinical Neurophysiology* 114 (2): 171–83. https://doi.org/10.1016/s1388-2457(02)00362-0.

Barth, Michael, Levente Kriston, Swaantje Klostermann, Corrado Barbui, Andrea Cipriani, and Klaus Linde. 2016. "Efficacy of Selective Serotonin Reuptake Inhibitors and Adverse Events: Meta-Regression and Mediation Analysis of Placebo-Controlled Trials." *British Journal of Psychiatry* 208 (2): 114–19. https://doi.org/10.1192/bjp.bp.114.150136.

Başar, Erol, Canan Başar-Eroglu, Sirel Karakaş, and Martin Schürmann. 2001. "Gamma, Alpha, Delta, and Theta Oscillations Govern Cognitive Processes." *International Journal of Psychophysiology* 39 (2–3): 241–48. https://doi.org/10.1016/s0167-8760(00)00145-8.

Bassett, Danielle S., and Edward T. Bullmore. 2009. "Human Brain Networks in Health and Disease." *Current Opinion in Neurology* 22 (4): 340–47. https://doi.org/10.1097/wco.0b013e32832d93dd.

Bauducco, Serena V., Selma Salihovic, and Katja Boersma. 2019. "Bidirectional Associations between Adolescents' Sleep Problems and Impulsive Behavior over Time." *Sleep Medicine*: X 1: 100009. https://doi.org/10.1016/j.sleepx.2019.100009.

Belmaker, R. H., and Galila Agam. 2008. "Major Depressive Disorder." *New England Journal of Medicine* 358 (1): 55–68. https://doi.org/10.1056/nejmra073096.

Belujon, Pauline, and Anthony A. Grace. 2017. "Dopamine System Dysregulation in Major Depressive Disorders." *The International Journal of Neuropsychopharmacology* 20 (12): 1036–46. https://doi.org/10.1093/ijnp/pyx05.

Berger, Hans. 1929. "Über Das Elektrenkephalogramm Des Menschen." *Archiv Für Psychiatrie Und Nervenkrankheiten* 87 (1): 527–70. https://doi.org/10.1007/bf01797193.

Blum, Kenneth, Amanda Lih-Chuan Chen, Eric R. Braverman, David E. Comings, Thomas J. H. Chen, Vanessa Arcuri, Seth H. Blum, et al. 2008. "Attention-Deficit-Hyperactivity Disorder and Reward Deficiency Syndrome." *Neuropsychiatric Disease and Treatment* 4 (5): 893–918. https://doi.org/10.2147/ndt.s2627.

Blume, Warren T. 2006. "Drug Effects on EEG." *Journal of Clinical Neurophysiology* 23 (4): 306–11. https://doi.org/10.1097/01.wnp.0000229137.94384.fa.

Bornovalova, Marina A., C.W. Lejuez, Stacey B. Daughters, M. Zachary Rosenthal, and Thomas R. Lynch. 2005. "Impulsivity as a Common Process across Borderline

Personality and Substance Use Disorders." *Clinical Psychology Review* 25 (6): 790–812. https://doi.org/10.1016/j.cpr.2005.05.005.

Bruder, Gerard E., Craig E. Tenke, and Jürgen Kayser. 2013. "Electrophysiological Predictors of Clinical Response to Antidepressants." In *Clinical Handbook for the Management of Mood Disorders*, edited by J. John Mann, Patrick J. McGrath, and Steven P. Roose, 380–93. New York: Cambridge University Press. https://doi.org/10.1017/cbo9781139175869.030.

Bruder, Gerard E., James P. Sedoruk, Jonathan W. Stewart, Patrick J. McGrath, Frederic M. Quitkin, and Craig E. Tenke. 2008. "Electroencephalographic Alpha Measures Predict Therapeutic Response to a Selective Serotonin Reuptake Inhibitor Antidepressant: Pre- and Post-Treatment Findings." *Biological Psychiatry* 63 (12): 1171–77. https://doi.org/10.1016/j.biopsych.2007.10.009.

Bruder, Gerard E., Jonathan W. Stewart, Craig E. Tenke, Patrick J. McGrath, Paul Leite, Nil Bhattacharya, and Frederic M. Quitkin. 2001. "Electroencephalographic and Perceptual Asymmetry Differences between Responders and Nonresponders to an SSRI Antidepressant." *Biological Psychiatry* 49 (5): 416–25. https://doi.org/10.1016/s0006-3223(00)01016-7.

Bruder, Gerard E., Regan Fong, Craig E. Tenke, Paul Leite, James P. Towey, Jonathan E. Stewart, Patrick J. McGrath, and Frederic M. Quitkin. 1997. "Regional Brain Asymmetries in Major Depression with or without an Anxiety Disorder: A Quantitative Electroencephalographic Study." *Biological Psychiatry* 41 (9): 939–48. https://doi.org/10.1016/s0006-3223(96)00260-0.

Bučková, Barbora, Martin Brunovský, Martin Bareš, and Jaroslav Hlinka. 2020. "Predicting Sex From EEG: Validity and Generalizability of Deep-Learning-Based Interpretable Classifier." *Frontiers in Neuroscience* 14: 589303. https://doi.org/10.3389/fnins.2020.589303.

Calhoun, Vince D., Jingyu Liu, and Tülay Adali. 2009. "A Review of Group ICA for fMRI Data and ICA for Joint Inference of Imaging, Genetic, and ERP Data." *Neuro Image* 45 (1 Suppl): S163-172. https://doi.org/10.1016/j.neuroimage.2008.10.057.

Carlo, Vera De, Raffaella Calati, and Alessandro Serretti. 2016. "Socio-Demographic and Clinical Predictors of Non-Response/Non-Remission in Treatment Resistant Depressed Patients: A Systematic Review." *Psychiatry Research* 240 (Int. J. *Neuro psychopharmacol*. 6 2003): 421–30. https://doi.org/10.1016/j.psychres.2016.04.034.

Chabot, Robert J., and Gordon Serfontein. 1996. "Quantitative Electroencephalographic Profiles of Children with Attention Deficit Disorder." *Biological Psychiatry* 40 (10): 951–63. https://doi.org/10.1016/0006-3223(95)00576-5.

Chabot, Robert J., ORgill A. Anna, Crawford Geoff, Harris J. Michael, and Serfontein Gordon. 1999. "Behavioral and Electrophysiologic Predictors of Treatment Response to Stimulants in Children with Attention Disorders." *Journal of Child Neurology*, 14: 343–51.

Chang, Christopher C., Carson C. Chow, Laurent Cam Tellier, Shashaank Vattikuti, Shaun M. Purcell, and James J. Lee. 2015. "Second-Generation PLINK: Rising to the Challenge of Larger and Richer Datasets." *GigaScience* 4: 7. https://doi.org/10.1186/s13742-015-0047-8.

Chiang, A.K.I., C.J. Rennie, P.A. Robinson, S.J. van Albada, and C.C. Kerr. 2011. "Age Trends and Sex Differences of Alpha Rhythms Including Split Alpha Peaks." *Clinical Neurophysiology* 122 (8): 1505–17. https://doi.org/10.1016/j.clinph.2011.01.040.

Choi, Shing Wan, and Paul F. O'Reilly. 2019. "PRSice-2: Polygenic Risk Score Software

for Biobank-Scale Data." *GigaScience* 8 (7): giz082. https://doi.org/10.1093/gigascience/giz082.
Choi, Shing Wan, Timothy Shin-Heng Mak, and Paul F. O'Reilly. 2020. "Tutorial: A Guide to Performing Polygenic Risk Score Analyses." *Nature Protocols* 15 (9): 2759–72. https://doi.org/10.1038/s41596-020-0353-1.
Choi, Won-Seok, Young Sup Woo, Sheng-Min Wang, Hyun Kook Lim, and Won-Myong Bahk. 2022. "The Prevalence of Psychiatric Comorbidities in Adult ADHD Compared with Non-ADHD Populations: A Systematic Literature Review." *PLOS ONE* 17 (11): e0277175. https://doi.org/10.1371/journal.pone.0277175.
Cipriani, Andrea, Teresa La Ferla, Toshi A Furukawa, Alessandra Signoretti, Atsuo Nakagawa, Rachel Churchill, Hugh McGuire, and Corrado Barbui. 2010. "Sertraline versus Other Antidepressive Agents for Depression." *Cochrane Database of Systematic Reviews*, no. 4: CD006117. https://doi.org/10.1002/14651858.cd006117.pub4.
Clarke, Adam R., Robert J. Barry, Dominique Bond, Rory McCarthy, and Mark Selikowitz. 2002. "Effects of Stimulant Medications on the EEG of Children with Attention-Deficit/Hyperactivity Disorder." *Psychopharmacology* 164 (3): 277–84. https://doi.org/10.1007/s00213-002-1205-0.
Clarke, Adam R., Robert J. Barry, Franca E. Dupuy, Rory McCarthy, Mark Selikowitz, and Stuart J. Johnstone. 2013. "Excess Beta Activity in the EEG of Children with Attention-Deficit/Hyperactivity Disorder: A Disorder of Arousal?" *International Journal of Psychophysiology* 89 (3): 314–19. https://doi.org/10.1016/j.ijpsycho.2013.04.009.
Clarke, Adam R., Robert J. Barry, Rory McCarthy, and Mark Selikowitz. 1998. "EEG Analysis in Attention-Deficit/Hyperactivity Disorder: A Comparative Study of Two Subtypes." *Psychiatry Research* 81 (1): 19–29. https://doi.org/10.1016/s0165-1781(98)00072-9.
Clarke, Adam R., Robert J. Barry, Rory McCarthy, and Mark Selikowitz. 2001a. "Age and Sex Effects in the EEG: Development of the Normal Child." *Clinical Neurophysiology* 112 (5): 806–14. https://doi.org/10.1016/s1388-2457(01)00488-6.
Clarke, Adam R., Robert J. Barry, Rory McCarthy, and Mark Selikowitz. 2001b. "Electroencephalogram Differences in Two Subtypes of Attention-Deficit/Hyperactivity Disorder." *Psychophysiology* 38 (2): 212–21. https://doi.org/10.1111/1469-8986.3820212.
Clarke, Adam R., Robert J. Barry, Rory McCarthy, and Mark Selikowitz. 2001c. "Excess Beta Activity in Children with Attention-Deficit/Hyperactivity Disorder: An Atypical Electrophysiological Group." *Psychiatry Research* 103 (2–3): 205–18. https://doi.org/10.1016/s0165-1781(01)00277-3.
Clarke, Adam R., Robert J. Barry, Rory McCarthy, Mark Selikowitz, Donna C. Clarke, and Rodney J. Croft. 2003. "Effects of Stimulant Medications on Children with Attention-Deficit/Hyperactivity Disorder and Excessive Beta Activity in Their EEG." *Clinical Neurophysiology* 114 (9): 1729–37. https://doi.org/10.1016/s1388-2457(03)00112-3.
Clarke, Adam R., Robert J. Barry, Rory McCarthy, Mark Selikowitz, and Stuart J. Johnstone. 2007. "Effects of Stimulant Medications on the EEG of Girls with Attention-Deficit/Hyperactivity Disorder." *Clinical Neurophysiology* 118 (12): 2700–2708. https://doi.org/10.1016/j.clinph.2007.08.020.
Comon, Pierre. 1994. "Independent Component Analysis, A New Concept?" *Signal Processing* 36 (3): 287–314. https://doi.org/10.1016/0165-1684(94)90029-9.

Cortese, Samuele, Stephen V. Faraone, Silvia Bernardi, Shuai Wang, and Carlos Blanco. 2016. "Gender Differences in Adult Attention-Deficit/Hyperactivity Disorder." *The Journal of Clinical Psychiatry* 77 (04): e421–28. https://doi.org/10.4088/jcp.14m09630.

Crisp, Zharia C., and Jon E. Grant. 2024. "Impulsivity across Psychiatric Disorders in Young Adults." *Comprehensive Psychiatry* 130: 152449. https://doi.org/10.1016/j.comppsych.2023.152449.

Cuthbert, Bruce N., and Thomas R. Insel. 2013. "Toward the Future of Psychiatric Diagnosis: The Seven Pillars of RDoC." *BMC Medicine* 11 (1): 126. https://doi.org/10.1186/1741-7015-11-126.

Dahl, Ronald E. 1996. "The Regulation of Sleep and Arousal: Development and Psychopathology." *Development and Psychopathology* 8 (1): 3–27. https://doi.org/10.1017/s0954579400006945.

Das, Sayantan, Lukas Forer, Sebastian Schönherr, Carlo Sidore, Adam E. Locke, Alan Kwong, Scott I. Vrieze, et al. 2016. "Next-Generation Genotype Imputation Service and Methods." *Nature Genetics* 48 (10): 1284–87. https://doi.org/10.1038/ng.3656.

Dauvilliers, Yves, Mehdi Tafti, and Hans Peter Landolt. 2015. "Catechol-O-Methyltransferase, Dopamine, and Sleep-Wake Regulation." *Sleep Medicine Reviews* 22: 47–53. https://doi.org/10.1016/j.smrv.2014.10.006.

De, Rishika, William S. Bush, and Jason H. Moore. 2014. "Bioinformatics Challenges in Genome-Wide Association Studies (GWAS)." In *Clinical Bioinformatics*, edited by R. Trent, 1168:63–81. Methods in Molecular Biology. New York: Humana Press. https://doi.org/10.1007/978-1-4939-0847-9_5.

Demyttenaere, Koen, Paul Enzlin, Walthere Dewe, Bruno Boulanger, Jozef De Bie, Wim De Troyer, and Patrick Mesters. 2001. "Compliance With Antidepressants in a Primary Care Setting, 1: Beyond Lack of Efficacy and Adverse Events." *The Journal of Clinical Psychiatry* 62 (Suppl 22): 30–33.

Dijk, Hanneke van, Guido van Wingen, Damiaan Denys, Sebastian Olbrich, Rosalinde van Ruth, and Martijn Arns. 2022. "The Two Decades Brainclinics Research Archive for Insights in Neurophysiology (TDBRAIN) Database." *Scientific Data*, 9 (1): 333. https://doi.org/10.1038/s41597-022-01409-z.

Dinteren, Rik van, Martijn Arns, Leon Kenemans, Marijtje L. A. Jongsma, Roy P. C. Kessels, Paul Fitzgerald, Kamran Fallahpour, Charles Debattista, Evian Gordon, and Leanne M. Williams. 2015. "Utility of Event-Related Potentials in Predicting Antidepressant Treatment Response: An iSPOT-D Report." *European Neuropsychopharmacology* 25 (11): 1981–90. https://doi.org/10.1016/j.euroneuro.2015.07.022.

Donse, Lana, Frank Padberg, Alexander T. Sack, A. John Rush, and Martijn Arns. 2017. "Simultaneous rTMS and Psychotherapy in Major Depressive Disorder: Clinical Outcomes and Predictors from a Large Naturalistic Study." *Brain Stimulation* 11 (2): 337–45. https://doi.org/10.1016/j.brs.2017.11.004.

Drysdale, Andrew T., Logan Grosenick, Jonathan Downar, Katharine Dunlop, Farrokh Mansouri, Yue Meng, Robert N. Fetcho, et al. 2017. "Resting-State Connectivity Biomarkers Define Neurophysiological Subtypes of Depression." *Nature Medicine*, 23 (1): 28–38. https://doi.org/10.1038/nm.4246.

Dupuy, Franca E., Adam R. Clarke, Robert J. Barry, Rory McCarthy, and Mark Selikowitz. 2021. "DSM-5 Adult Attention-Deficit/Hyperactivity Disorder: Sex Differences in EEG Activity." *Applied Psychophysiology and Biofeedback* 46 (4): 377–88. https://doi.org/10.1007/s10484-021-09522-2.

Dupuy, Franca E., Robert J. Barry, Adam R. Clarke, Rory McCarthy, and Mark Selikowitz. 2013. "Sex Differences between the Combined and Inattentive Types of Attention-Deficit/Hyperactivity Disorder: An EEG Perspective." *International Journal of Psychophysiology* 89 (3): 320–27. https://doi.org/10.1016/j.ijpsycho.2013.04.004.

Eban-Rothschild, Ada, Gideon Rothschild, William J. Giardino, Jeff R. Jones, and Luis de Lecea. 2016. "VTA Dopaminergic Neurons Regulate Ethologically Relevant Sleep–Wake Behaviors." *Nature Neuroscience* 19 (10): 1356–66. https://doi.org/10.1038/nn.4377.

Erguzel, Turker Tekin, Serhat Ozekes, Selahattin Gultekin, Nevzat Tarhan, Gokben Hizli Sayar, and Ali Bayram. 2014. "Neural Network Based Response Prediction of rTMS in Major Depressive Disorder Using QEEG Cordance." *Psychiatry Investigation* 12 (1): 61–65. https://doi.org/10.4306/pi.2015.12.1.61.

Etkin, Amit, Brian Patenaude, Yun Ju C Song, Timothy Usherwood, William Rekshan, Alan F Schatzberg, A. John Rush, and Leanne M Williams. 2015. "A Cognitive–Emotional Biomarker for Predicting Remission with Antidepressant Medications: A Report from the iSPOT-D Trial." *Neuropsychopharmacology* 40 (6): 1332–42. https://doi.org/10.1038/npp.2014.333.

Fabbri, Chiara, Katherine E. Tansey, Roy H. Perlis, Joanna Hauser, Neven Henigsberg, Wolfgang Maier, Ole Mors, et al. 2018. "New Insights into the Pharmacogenomics of Antidepressant Response from the GENDEP and STAR*D Studies: Rare Variant Analysis and High-Density Imputation." *The Pharmacogenomics Journal* 18 (3): 413–21. https://doi.org/10.1038/tpj.2017.44.

Fabbri, Chiara, Stuart Montgomery, Cathryn M. Lewis, and Alessandro Serretti. 2020. "Genetics and Major Depressive Disorder: Clinical Implications for Disease Risk, Prognosis and Treatment." *International Clinical Psychopharmacology* 35 (5): 233–42. https://doi.org/10.1097/yic.0000000000000305.

Fanelli, Giuseppe, Francesco Benedetti, Siegfried Kasper, Joseph Zohar, Daniel Souery, Stuart Montgomery, Diego Albani, et al. 2020. "Higher Polygenic Risk Scores for Schizophrenia May Be Suggestive of Treatment Non-Response in Major Depressive Disorder." *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 110170. https://doi.org/10.1016/j.pnpbp.2020.110170.

Fanelli, Giuseppe, Katharina Domschke, Alessandra Minelli, Massimo Gennarelli, Paolo Martini, Marco Bortolomasi, Eduard Maron, et al. 2022. "A Meta-Analysis of Polygenic Risk Scores for Mood Disorders, Neuroticism, and Schizophrenia in Antidepressant Response." *European Neuropsychopharmacology* 55: 86–95. https://doi.org/10.1016/j.euroneuro.2021.11.005.

Figiel, Gary S., Charles Epstein, William M. McDonald, Jody Amazon-Leece, Linda Figiel, Aida Saldivia, and Susan Glover. 1998. "The Use of Rapid-Rate Transcranial Magnetic Stimulation (rTMS) in Refractory Depressed Patients." *The Journal of Neuropsychiatry and Clinical Neurosciences* 10 (1): 20–25. https://doi.org/10.1176/jnp.10.1.20.

Fingelkurts, Alexander A., Andrew A. Fingelkurts, Heikki Rytsälä, Kirsi Suominen, Erkki Isometsä, and Seppo Kähkönen. 2006. "Composition of Brain Oscillations in Ongoing EEG during Major Depression Disorder." *Neuroscience Research* 56 (2): 133–44. https://doi.org/10.1016/j.neures.2006.06.006.

Firth, Nick, Michael Barkham, and Stephen Kellett. 2015. "The Clinical Effectiveness of Stepped Care Systems for Depression in Working Age Adults: A Systematic

Review." 2015. *https://eprints.whiterose.ac.uk/91872/3/Clinical Effectiveness.pdf*.
Flor-Henry, Pierre, John C. Lind, and Zoltan J. Koles. 2004. "A Source-Imaging (Low-Resolution Electromagnetic Tomography) Study of the EEGs from Unmedicated Males with Depression." *Psychiatry Research: Neuroimaging* 130 (2): 191–207. https://doi.org/10.1016/j.pscychresns.2003.08.006.
Fonseka, Trehani M., Glenda M. MacQueen, and Sidney H. Kennedy. 2018. "Neuroimaging Biomarkers as Predictors of Treatment Outcome in Major Depressive Disorder." *Journal of Affective Disorders* 233 (Transl. Psychiatry 4 2014): 21–35. https://doi.org/10.1016/j.jad.2017.10.049.
Foo, Jerome C., Fabian Streit, Josef Frank, Stephanie H. Witt, Jens Treutlein, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Bernhard T. Baune, et al. 2019. "Evidence for Increased Genetic Risk Load for Major Depression in Patients Assigned to Electroconvulsive Therapy." *American Journal of Medical Genetics* Part B Neuropsychiatric Genetics 180 (1): 35–45. https://doi.org/10.1002/ajmg.b.32700.
Fox, Michael D., Randy L. Buckner, Matthew P. White, Michael D. Greicius, and Alvaro Pascual-Leone. 2012. "Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate." *Biological Psychiatry* 72 (7): 595–603. https://doi.org/10.1016/j.biopsych.2012.04.028.
Freedman, Alfred M. 1995. "The Biopsychosocial Paradigm and the Future of Psychiatry." *Comprehensive Psychiatry* 36 (6): 397–406. https://doi.org/10.1016/s0010-440x(95)90246-5.
Furnham, Adrian. 1986. "Response Bias, Social Desirability and Dissimulation." *Personality and Individual Differences* 7 (3): 385–400. https://doi.org/10.1016/0191-8869(86)90014-0.
García-Gonzáleza, Judit, Katherine E. Tansey, Joanna Hauser, Neven Henigsberg, Wolfgang Maier, Ole Mors, Anna Placentino, et al. 2017. "Pharmacogenetics of Antidepressant Response: A Polygenic Approach." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 75: 128–34. https://doi.org/10.1016/j.pnpbp.2017.01.011.
Garriock, Holly A., Jeffrey B. Kraft, Stanley I. Shyn, Eric J. Peters, Jennifer S. Yokoyama, Gregory D. Jenkins, Megan S. Reinalda, Susan L. Slager, Patrick J. McGrath, and Steven P. Hamilton. 2010. "A Genome-Wide Association Study of Citalopram Response in Major Depressive Disorder." *Biological Psychiatry* 67 (2): 133–38. https://doi.org/10.1016/j.biopsych.2009.08.029.
Gerrits, Berrie, Madelon A. Vollebregt, Sebastian Olbrich, Hanneke van Dijk, Donna Palmer, Evian Gordon, Roberto Pascual-Marqui, Roy P. C. Kessels, and Martijn Arns. 2019. "Probing the 'Default Network Interference Hypothesis' With EEG: An RDoC Approach Focused on Attention." *Clinical EEG and Neuroscience* 50 (6): 404–12. https://doi.org/10.1177/1550059419864461.
Gibbs, F. A., H. Davis, and W. G. Lennox. 1935. "The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness." *Archives of Neurology & Psychiatry* 34 (6): 1133–48. https://doi.org/10.1001/archneurpsyc.1935.02250240002001.
Goethe, John W., Stephen B. Woolley, Alex A. Cardoni, Brenda A. Woznicki, and Deborah A. Piez. 2007. "Selective Serotonin Reuptake Inhibitor Discontinuation: Side Effects and Other Factors That Influence Medication Adherence." *Journal of Clinical Psychopharmacology* 27 (5): 451–58. https://doi.org/10.1097/jcp.0b013e31815152a5.

Gramfort, Alexandre, Martin Luessi, Eric Larson, Denis A. Engemann, Daniel Strohmeier, Christian Brodbeck, Roman Goj, et al. 2013. "MEG and EEG Data Analysis with MNE-Python." *Frontiers in Neuroscience* 7: 267. https://doi.org/10.3389/fnins.2013.00267.

Gratton, Gabriele, Michael G. H. Coles, and Emanuel Donchin. 1983. "A New Method for Off-Line Removal of Ocular Artifact." *Electroencephalography and Clinical Neurophysiology* 55 (4): 468–84. https://doi.org/10.1016/0013-4694(83)90135-9.

Grin-Yatsenko, Vera A., Ineke Baas, Valery A. Ponomarev, and Juri D. Kropotov. 2010. "Independent Component Approach to the Analysis of EEG Recordings at Early Stages of Depressive Disorders." *Clinical Neurophysiology* 121 (3): 281–89. https://doi.org/10.1016/j.clinph.2009.11.015.

Hack, Laura M., Leonardo Tozzi, Samantha Zenteno, Alisa M. Olmsted, Rachel Hilton, Jenna Jubeir, Mayuresh S. Korgaonkar, et al. 2023. "A Cognitive Biotype of Depression and Symptoms, Behavior Measures, Neural Circuits, and Differential Treatment Outcomes." *JAMA Network Open* 6 (6): e2318411. https://doi.org/10.1001/jamanetworkopen.2023.18411.

Haegens, Saskia, Helena Cousijn, George Wallis, Paul J. Harrison, and Anna C. Nobre. 2014. "Inter- and Intra-Individual Variability in Alpha Peak Frequency." *NeuroImage* 92: 1–10. https://doi.org/10.1016/j.neuroimage.2014.01.049.

Hallgren, Kevin A. 2012. "Computing Inter-Rater Reliability for Observational Data: An Overview and Tutorial." *Tutorials in Quantitative Methods for Psychology* 8 (1): 23–34.

Hanlon, Colleen A., and Daniel M. McCalley. 2022. "Sex/Gender as a Factor That Influences Transcranial Magnetic Stimulation Treatment Outcome: Three Potential Biological Explanations." *Frontiers in Psychiatry* 13: 869070. https://doi.org/10.3389/fpsyt.2022.869070.

Harrison, Yvonne, and James A. Horne. 2000. "The Impact of Sleep Deprivation on Decision Making: A Review." *Journal of Experimental Psychology*: Applied 6 (3): 236–49. https://doi.org/10.1037//1076-898x.6.3.236.

Hartung, Thomas, Sebastian Hoffmann, and Martin Stephens. 2013. "Mechanistic Validation." *Alternativen Zu Tierexperimenten* 30 (2): 119–30. https://doi.org/10.14573/altex.2013.2.11.

Hasanzadeh, Fatemeh, Maryam Mohebbi, and Reza Rostami. 2019. "Prediction of rTMS Treatment Response in Major Depressive Disorder Using Machine Learning Techniques and Nonlinear Features of EEG Signal." *Journal of Affective Disorders* 256: 132–42. https://doi.org/10.1016/j.jad.2019.05.070.

Hasson, Ramzi, and Jodene Goldenring Fine. 2012. "Gender Differences Among Children With ADHD on Continuous Performance Tests." *Journal of Attention Disorders* 16 (3): 190–98. https://doi.org/10.1177/1087054711427398.

Hayes, Andrew F. 2020. "The PROCESS Macro for SPSS, SAS, and R." 2020. http://www.processmacro.org/index.html.

Hegerl, Ulrich, Kathrin Wilk, Sebastian Olbrich, Peter Schoenknecht, and Christian Sander. 2011. "Hyperstable Regulation of Vigilance in Patients with Major Depressive Disorder." *The World Journal of Biological Psychiatry* 13 (6): 436–46. https://doi.org/10.3109/15622975.2011.579164.

Hegerl, Ulrich, Michael Stein, Christoph Mulert, Roland Mergl, Sebastian Olbrich, Eva Dichgans, Dan Rujescu, and Oliver Pogarell. 2008. "EEG-Vigilance Differences between Patients with Borderline Personality Disorder, Patients with Obses

sive-Compulsive Disorder and Healthy Controls." *European Archives of Psychiatry and Clinical Neuroscience* 258 (3): 137–43. https://doi.org/10.1007/s00406-007-0765-8.
Henriques, Jeffrey B., and Richard J. Davidson. 1990. "Regional Brain Electrical Asymmetries Discriminate between Previously Depressed and Healthy Control Subjects." *Journal of Abnormal Psychology* 99 (1): 22–31. https://doi.org/10.1037/0021-843x.99.1.22.
Hodgson, Karen, Shaista Jeelani Mufti, Rudolf Uher, and Peter McGuffin. 2012. "Genome-Wide Approaches to Antidepressant Treatment: Working towards Understanding and Predicting Response." *Genome Medicine* 4 (6): 52. https://doi.org/10.1186/gm351.
Huang, Chih-Chia, I-Hua Wei, Yuan-Hwa Chou, and Tung-Ping Su. 2018. "Effect of Age, Gender, Menopausal Status, and Ovarian Hormonal Level on rTMS in Treatment-Resistant Depression." *Psychoneuroendocrinology* 33 (6): 821–31. https://doi.org/10.1016/j.psyneuen.2008.03.00.
Hughes, John R., and E. Roy John. 1999. "Conventional and Quantitative Electroencephalography in Psychiatry." *The Journal of Neuropsychiatry and Clinical Neurosciences* 11 (2): 190–208. https://doi.org/10.1176/jnp.11.2.190.
IBM SPSS Statistics for Macintosh (Version 27.0). 2020. Armonk, NY: IBM Corp.
Insel, Thomas, Bruce Cuthbert, Marjorie Garvey, Robert Heinssen, Daniel S. Pine, Kevin Quinn, Charles Sanislow, and Philip Wang. 2010. "Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders." *American Journal of Psychiatry*, 167 (7): 748–51. https://doi.org/10.1176/appi.ajp.2010.09091379.
Iseger, Tabitha A., Mayuresh S. Korgaonkar, J. Leon Kenemans, Stuart M. Grieve, Chris Baeken, Paul B. Fitzgerald, and Martijn Arns. 2017. "EEG Connectivity between the Subgenual Anterior Cingulate and Prefrontal Cortices in Response to Antidepressant Medication." *European Neuropsychopharmacology* 27 (4): 301–12. https://doi.org/10.1016/j.euroneuro.2017.02.002.
Iseger, Tabitha A., Nienke E. R. van Bueren, J. Leon Kenemans, Richard Gevirtz, and Martijn Arns. 2020. "A Frontal-Vagal Network Theory for Major Depressive Disorder: Implications for Optimizing Neuromodulation Techniques." *Brain Stimulation* 13 (1): 1–9. https://doi.org/10.1016/j.brs.2019.10.006.
Ising, Marcus, Susanne Lucae, Elisabeth B. Binder, Thomas Bettecken, Manfred Uhr, Stephan Ripke, Martin A. Kohli, et al. 2009. "A Genome-Wide Association Study Points to Multiple Loci Predicting Antidepressant Treatment Outcome in Depression." *Archives Of General Psychiatry* 66 (9): 966–75. https://doi.org/10.1001/archgenpsychiatry.2009.95.
Jatoi, Munsif Ali, Nidal Kamel, Aamir Saeed Malik, Ibrahima Faye, and Tahamina Begum. 2014. "A Survey of Methods Used for Source Localization Using EEG Signals." *Biomedical Signal Processing and Control* 11: 42–52. https://doi.org/10.1016/j.bspc.2014.01.009.
Jenkinson, Ned, and Peter Brown. 2011. "New Insights into the Relationship between Dopamine, Beta Oscillations and Motor Function." *Trends in Neurosciences* 34 (12): 611–18. https://doi.org/10.1016/j.tins.2011.09.003.
Ji, Yuan, Joanna M. Biernacka, Scott Hebbring, Yubo Chai, Gregory D. Jenkins, Anthony Batzler, Karen A. Snyder, et al. 2013. "Pharmacogenomics of Selective Serotonin Reuptake Inhibitor Treatment for Major Depressive Disorder: Genome-Wide Associations and Functional Genomics." *The Pharmacogenomics*

Journal 13 (5): 456–63. https://doi.org/10.1038/tpj.2012.32.
Jochmann, Thomas, Marc S. Seibel, Elisabeth Jochmann, Sheraz Khan, Matti S. Hämäläinen, and Jens Haueisen. 2023. "Sex-related Patterns in the Electroencephalogram and Their Relevance in Machine Learning Classifiers." *Human Brain Mapping*. https://doi.org/10.1002/hbm.26417.
Johnson, Lise A., Tim Blakely, Dora Hermes, Shahin Hakimian, Nick F. Ramsey, and Jeffrey G. Ojemann. 2012. "Sleep Spindles Are Locally Modulated by Training on a Brain–Computer Interface." *Proceedings of the National Academy of Sciences* 109 (45): 18583–88. https://doi.org/10.1073/pnas.1207532109.
Johnstone, J., J. Gunkelman, and J. Lunt. 2005. "Clinical Database Development: Characterization of EEG Phenotypes." *Clinical EEG and Neuroscience* 36 (2): 99–107. https://doi.org/10.1177/155005940503600209.
Katzman, Martin A., Timothy S. Bilkey, Pratap R. Chokka, Angelo Fallu, and Larry J Klassen. 2017. "Adult ADHD and Comorbid Disorders: Clinical Implications of a Dimensional Approach." *BMC Psychiatry* 17 (1): 302. https://doi.org/10.1186/s12888-017-1463-3.
Kaźmierczak, Marcin, and Saleem M. Nicola. 2022. "The Arousal-Motor Hypothesis of Dopamine Function: Evidence That Dopamine Facilitates Reward Seeking in Part by Maintaining Arousal." *Neuroscience* 499: 64–103. https://doi.org/10.1016/j.neuroscience.2022.07.008.
Kedzior, Karina Karolina, Valeriya Azorina, and Sarah Kim Reitz. 2014. "More Female Patients and Fewer Stimuli per Session Are Associated with the Short-Term Antidepressant Properties of Repetitive Transcranial Magnetic Stimulation (rTMS): A Meta-Analysis of 54 Sham-Controlled Studies Published between 1997–2013." *Neuropsychiatric Disease and Treatment* 10: 727–56. https://doi.org/10.2147/ndt.s58405.
Kember, Rachel L., Alison K. Merikangas, Shefali S. Verma, Anurag Verma, Renae Judy, Scott M. Damrauer, Marylyn D. Ritchie, et al. 2021. "Polygenic Risk of Psychiatric Disorders Exhibits Cross-Trait Associations in Electronic Health Record Data From European Ancestry Individuals." *Biological Psychiatry* 89 (3): 236–45. https://doi.org/10.1016/j.biopsych.2020.06.026.
Kenneth, Blum, Oscar-Berman Marlene, Badgaiyan Rajendra, A Khurshid Khurshid, and S Gold Mark. 2014. "Dopaminergic Neurogenetics of Sleep Disorders in Reward Deficiency Syndrome (RDS)." *Journal of Sleep Disorders & Therapy* 03 (02): 126. https://doi.org/10.4172/2167-0277.1000e126.
Kesner, Andrew J., and David M. Lovinger. 2021. "Wake up and Smell the Dopamine: New Mechanisms Mediating Dopamine Activity Fluctuations Related to Sleep and Psychostimulant Sensitivity." *Neuropsychopharmacology* 46 (4): 683–84. https://doi.org/10.1038/s41386-020-00903-5.
Kim, Soyoun, and Daeyeol Lee. 2011. "Prefrontal Cortex and Impulsive Decision Making." *Biological Psychiatry* 69 (12): 1140–46. https://doi.org/10.1016/j.biopsych.2010.07.005.
Kitaichi, Yuji, Takeshi Inoue, Shin Nakagawa, Shuken Boku, Aya Kakuta, Takeshi Izumi, and Tsukasa Koyama. 2010. "Sertraline Increases Extracellular Levels Not Only of Serotonin, but Also of Dopamine in the Nucleus Accumbens and Striatum of Rats." *European Journal of Pharmacology* 647 (1–3): 90–96. https://doi.org/10.1016/j.ejphar.2010.08.026.
Klem, G., H. Lüders, H. Jasper, and C. Elger. 1999. "The Ten-Twenty Electrode System

of the International Federation. The International Federation of Clinical Neurophysiology." *Electroencephalography and Clinical Neurophysiology* 52: 3–6.
Klimesch, Wolfgang. 1999. "EEG Alpha and Theta Oscillations Reflect Cognitive and Memory Performance: A Review and Analysis." *Brain Research Reviews* 29 (2–3): 169–95. https://doi.org/10.1016/s0165-0173(98)00056-3.
Klooster, Debby, Helena Voetterl, Chris Baeken, and Martijn Arns. 2023. "Evaluating Robustness of Brain Stimulation Biomarkers for Depression: A Systematic Review of MRI and EEG Studies." *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2023.09.009.
Koudys, Jacob W., Cody Cane, Yuliya S. Nikolova, and Anthony C. Ruocco. 2023. "Transdiagnostic Impulsivity-Relevant Phenotypes and the Comorbidity of Personality Disorders with Substance and Alcohol Use Disorders." *Current Addiction Reports* 10 (2): 122–30. https://doi.org/10.1007/s40429-023-00483-6.
Krepel, Noralie, A. John Rush, Tabitha A. Iseger, Alexander T. Sack, and Martijn Arns. 2019. "Can Psychological Features Predict Antidepressant Response to rTMS? A Discovery–Replication Approach." *Psychological Medicine* 50 (2): 264–72. https://doi.org/10.1017/s0033291718004191.
Krepel, Noralie, Hanneke van Dijk, Alexander T. Sack, Ronald J. Swatzyna, and Martijn Arns. 2021. "To Spindle or Not to Spindle: A Replication Study Into Spindling Excessive Beta as a Transdiagnostic EEG Feature Associated with Impulse Control." *Biological Psychology*, 108188. https://doi.org/10.1016/j.biopsycho.2021.108188.
Kubicki, St., and A. Ascona. 1983. "Bases Genetiques Des Modeles Beta de l'EEG Du Sujet Adulte." *Revue d'Electroencéphalographie et de Neurophysiologie Clinique* 13 (3): 245–52. https://doi.org/10.1016/s0370-4475(83)80035-5.
Labaka, Ainitze, Olatz Goñi-Balentziaga, Andrea Lebeña, and Joana Pérez-Tejada. 2018. "Biological Sex Differences in Depression: A Systematic Review." *Biological Research For Nursing* 20 (4): 383–92. https://doi.org/10.1177/1099800418776082.
Lam, Raymond W., Peter Chan, Michael Wilkins-Ho, and Lakshmi N. Yatham. 2008. "Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Metaanalysis." *The Canadian Journal of Psychiatry* 53 (9): 621–31. https://doi.org/10.1177/070674370805300909.
LeCun, Yann, Yoshua Bengio, and Geoffrey Hinton. 2015. "Deep Learning." *Nature* 521 (7553): 436–44. https://doi.org/10.1038/nature14539.
LeGates, Tara A., Mark D. Kvarta, and Scott M. Thompson. 2019. "Sex Differences in Antidepressant Efficacy." *Neuropsychopharmacology* 44 (1): 140–54. https://doi.org/10.1038/s41386-018-0156-z.
Lewis, Cathryn M., and Evangelos Vassos. 2020. "Polygenic Risk Scores: From Research Tools to Clinical Instruments." *Genome Medicine*. https://doi.org/10.1186/s13073-020-00742-5.
Li, Qingqin S., Chao Tian, David Hinds, and 23andMe Research Team. 2020. "Genome-Wide Association Studies of Antidepressant Class Response and Treatment-Resistant Depression." *Translational Psychiatry* 10 (1): 360. https://doi.org/10.1038/s41398-020-01035-6.
Li, Qingqin S., Chao Tian, Guy R. Seabrook, Wayne C. Drevets, and Vaibhav A. Narayan. 2016. "Analysis of 23andMe Antidepressant Efficacy Survey Data: Implication of Circadian Rhythm and Neuroplasticity in Bupropion Response." *Translational Psychiatry* 6 (9): e889–e889. https://doi.org/10.1038/tp.2016.171.
Li, Qingqin S., Ewa Wajs, Rachel Ochs-Ross, Jaskaran Singh, and Wayne C. Drevets.

2020. "Genome-Wide Association Study and Polygenic Risk Score Analysis of Esketamine Treatment Response." *Scientific Reports* 10 (1): 12649. https://doi.org/10.1038/s41598-020-69291-6.

Lin, Bochao, Martijn Arns, Bart Rutten, Evian Gordon, and Jurjen J. Luykx. 2022. "Independent Replication and Drug-Specificity of an Antidepressant Response Polygenic Risk Score." *MedRxiv* [Preprint]. https://doi.org/10.1101/2022.04.29.22274313.

Liston, Conor, Ashley C. Chen, Benjamin D. Zebley, Andrew T. Drysdale, Rebecca Gordon, Bruce Leuchter, Henning U. Voss, B. J. Casey, Amit Etkin, and Marc J. Dubin. 2014. "Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression." *Biological Psychiatry* 76 (7): 517–26. https://doi.org/10.1016/j.biopsych.2014.01.023.

Luykx, Jurjen J., Dore Loef, Bochao Lin, Linda van Diermen, Jasper O. Nuninga, Eric van Exel, Mardien L. Oudega, et al. 2022. "Interrogating Associations Between Polygenic Liabilities and Electroconvulsive Therapy Effectiveness." *Biological Psychiatry* 91 (6): 531–39. https://doi.org/10.1016/j.biopsych.2021.10.013.

Mashour, George A., Dinesh Pal, and Emery N. Brown. 2022. "Prefrontal Cortex as a Key Node in Arousal Circuitry." *Trends in Neurosciences* 45 (10): 722–32. https://doi.org/10.1016/j.tins.2022.07.002.

Mason, Lynnette M., Robert J. Barry, and Adam R. Clarke. 2022. "Age-Related Changes in the EEG in an Eyes-Open Condition: I. Normal Development." *International Journal of Psychophysiology* 172: 40–45. https://doi.org/10.1016/j.ijpsycho.2021.11.005.

McLaughlin, Russell L., Dick Schijven, Wouter van Rheenen, Kristel R. van Eijk, Margaret O'Brien, René S. Kahn, Roel A. Ophoff, et al. 2017. "Genetic Correlation between Amyotrophic Lateral Sclerosis and Schizophrenia." *Nature Communications* 8: 14774. https://doi.org/10.1038/ncomms14774.

Meijs, Hannah, Amourie Prentice, Bochao D. Lin, Bieke De Wilde, Jan Van Hecke, Peter Niemegeers, Kristel van Eijk, Jurjen J. Luykx, and Martijn Arns. 2022. "A Polygenic-Informed Approach to a Predictive EEG Signature Empowers Antidepressant Treatment Prediction: A Proof-of-Concept Study." *European Neuropsychopharmacology* 62: 49–60. https://doi.org/10.1016/j.euroneuro.2022.07.006.

Meijs, Hannah, Helena Voetterl, Alexander T. Sack, Hanneke van Dijk, Bieke De Wilde, Jan Van Hecke, Peter Niemegeers, Evian Gordon, Jurjen J. Luykx, and Martijn Arns. 2024. "A Posterior-Alpha Ageing Network Is Differentially Associated with Antidepressant Effects of Venlafaxine and rTMS." *European Neuropsychopharmacology* 79: 7–16. https://doi.org/10.1016/j.euroneuro.2023.11.002.

Melgari, Jean-Marc, Giuseppe Curcio, Francesca Mastrolilli, Gaetano Salomone, Laura Trotta, Mario Tombini, Lazzaro di Biase, et al. 2014. "Alpha and Beta EEG Power Reflects L-Dopa Acute Administration in Parkinsonian Patients." *Frontiers in Aging Neuroscience* 6: 302. https://doi.org/10.3389/fnagi.2014.00302.

Michel, Christoph M., and Alvaro Pascual-Leone. 2020. "Predicting Antidepressant Response by Electroencephalography." *Nature Biotechnology* 38 (4): 417–19. https://doi.org/10.1038/s41587-020-0476-5.

Monti, Jaime M., and Héctor Jantos. 2008. "The Roles of Dopamine and Serotonin, and of Their Receptors, in Regulating Sleep and Waking." *Progress in Brain Research* 172: 625–46. https://doi.org/10.1016/s0079-6123(08)00929-1.

Morris, Sarah E., and Bruce N. Cuthbert. 2012. "Research Domain Criteria: Cognitive Systems, Neural Circuits, and Dimensions of Behavior." *Dialogues in Clinical*

Neuroscience 14 (1): 29–37.
Mullins, C. Daniel, Fadia T. Shaya, Fanlun Meng, Junling Wang, and David Harrison. 2005. "Persistence, Switching, and Discontinuation Rates Among Patients Receiving Sertraline, Paroxetine, and Citalopram." *Pharmacotherapy* 25 (5): 660–67. https://doi.org/10.1592/phco.25.5.660.63590.
Niedermeyer, Ernst, and Fernando Lopes da Silva. 1999. *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, edited by Charly Mitchell. 4th ed.
Nøhr, Anne Krogh, Annika Forsingdal, Ida Moltke, Oliver D. Howes, Morana Vitezic, Anders Albrechtsen, and Maria Dalby. 2022. "Polygenic Heterogeneity in Antidepressant Treatment and Placebo Response." *Translational Psychiatry* 12 (1): 456. https://doi.org/10.1038/s41398-022-02221-4.
Olbrich, Sebastian, and Martijn Arns. 2013. "EEG Biomarkers in Major Depressive Disorder: Discriminative Power and Prediction of Treatment Response." *International Review of Psychiatry* 25 (5): 604–18. https://doi.org/10.3109/09540261.2013.816269.
Olbrich, Sebastian, Anja Tränkner, Galina Surova, Richard Gevirtz, Evian Gordon, Ulrich Hegerl, and Martijn Arns. 2016. "CNS- and ANS-Arousal Predict Response to Antidepressant Medication: Findings from the Randomized lSPOT-D Study." *Journal of Psychiatric Research* 73: 108–15. https://doi.org/10.1016/j.jpsychires.2015.12.001.
Olbrich, Sebastian, Rik van Dinteren, and Martijn Arns. 2016. "Personalized Medicine: Review and Perspectives of Promising Baseline EEG Biomarkers in Major Depressive Disorder and Attention Deficit Hyperactivity Disorder." *Neuropsychobiology* 72 (3–4): 229–40. https://doi.org/10.1159/000437435.
Pain, Oliver, Karen Hodgson, Vassily Trubetskoy, Stephan Ripke, Victoria S. Marshe, Mark J. Adams, Enda M. Byrne, et al. 2020. "Antidepressant Response in Major Depressive Disorder: A Genome-Wide Association Study." *MedRxiv* [Preprint]. https://doi.org/10.1101/2020.12.11.20245035.
Pascual-Marqui, R. D., M. Esslen, K. Kochi, and D. Lehmann. 2002. "Functional Imaging with Low-Resolution Brain Electromagnetic Tomography (LORETA): A Review." *Methods and Findings in Experimental and Clinical Pharmacology* 24 Suppl C: 91–95.
Pascual-Marqui, Roberto D. 2007. "Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization", *arXiv:0710.3341* [math-ph]. http://arxiv.org/pdf/0710.3341.
Pascual-Marqui, Roberto D., and Rolando J. Biscay-Lirio. 2011. "Interaction Patterns of Brain Activity across Space, Time and Frequency. Part I: methods." arXiv:1103.2852v2 [stat.ME]. http://arxiv.org/abs/1103.2852.
Pascual-Marqui, Roberto D., Dietrich Lehmann, Martha Koukkou, Kieko Kochi, Peter Anderer, Bernd Saletu, Hideaki Tanaka, et al. 2011. "Assessing Interactions in the Brain with Exact Low-Resolution Electromagnetic Tomography." *Philosophical Transactions of the Royal Society* A 369: 3768–84. https://doi.org/10.1098/rsta.2011.0081.
Pedregosa, Fabian, Gaël Varoquaux, Alexandre Gramfort, Vincent Michel, Bertrand Thirion, Olivier Grisel, Mathieu Blondel, et al. 2012. "Scikit-Learn: Machine Learning in Python." *ArXiv*. https://doi.org/10.48550/arxiv.1201.0490.
Perlis, Michael L., Helli Merica, Michael T. Smith, and Donna E. Giles. 2001. "Beta EEG Activity and Insomnia." *Sleep Medicine Reviews* 5 (5): 363–74. https://doi.org/10.1053/smrv.2001.0151.

Polanczyk, Guilherme, Maurcio Silva de Lima, Bernardo Lessa Horta, Joseph Biederman, and Luis Augusto Rohde. 2007. "The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis." *American Journal of Psychiatry* 164 (6): 942–48. https://doi.org/10.1176/ajp.2007.164.6.942.

Purcell, Shaun M., Naomi R. Wray, Jennifer L. Stone, Peter M. Visscher, Michael C. O'Donovan, Patrick F. Sullivan, and Pamela Sklar. 2009. "Common Polygenic Variation Contributes to Risk of Schizophrenia and Bipolar Disorder." *Nature* 460 (7256): 748–52. https://doi.org/10.1038/nature08185.

Purcell, Shaun, Benjamin Neale, Kathe Todd-Brown, Lori Thomas, Manuel A. R. Ferreira, David Bender, Julian Maller, et al. 2007. "PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses." *American Journal of Human Genetics* 81 (3): 559–75. https://doi.org/10.1086/519795.

Putten, Michel J. A. M. van, Sebastian Olbrich, and Martijn Arns. 2018. "Predicting Sex from Brain Rhythms with Deep Learning." *Scientific Reports* 8 (1): 3069. https://doi.org/10.1038/s41598-018-21495-7.

Quinn, Patricia O, and Manisha Madhoo. 2014. "A Review of Attention-Deficit/Hyperactivity Disorder in Women and Girls: Uncovering This Hidden Diagnosis." *The Primary Care Companion For CNS Disorders* 16 (3). https://doi.org/10.4088/pcc.13r01596.

Ridding, Michael C., and John C. Rothwell. 2007. "Is There a Future for Therapeutic Use of Transcranial Magnetic Stimulation?" *Nature Reviews Neuroscience* 8 (7): 559–67. https://doi.org/10.1038/nrn2169.

Roelofs, Charlotte L., Noralie Krepel, Juliana Corlier, Linda L. Carpenter, Paul B. Fitzgerald, Zafiris J. Daskalakis, Indira Tendolkar, et al. 2020. "Individual Alpha Frequency Proximity Associated with Repetitive Transcranial Magnetic Stimulation Outcome: An Independent Replication Study from the ICON-DB Consortium." *Clinical Neurophysiology* 132 (2): 643–49. https://doi.org/10.1016/j.clinph.2020.10.017.

Roumen, Kirov, and Brand Serge. 2014. "Sleep Problems and Their Effect in ADHD." *Expert Review of Neurotherapeutics*, 14 (3): 287–99. https://doi.org/10.1586/14737175.2014.885382.

Rucklidge, Julia J. 2010. "Gender Differences in Attention-Deficit/Hyperactivity Disorder." *Psychiatric Clinics of North America* 33 (2): 357–73. https://doi.org/10.1016/j.psc.2010.01.006.

Rush, A. John, Madhukar H. Trivedi, Stephen R. Wisniewski, Andrew A. Nierenberg, Jonathan W. Stewart, Diane Warden, George Niederehe, et al. 2006. "Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report." *American Journal of Psychiatry* 163 (11): 1905–17. https://doi.org/10.1176/ajp.2006.163.11.1905.

Rush, A. John. 2007. "The Varied Clinical Presentations of Major Depressive Disorder." *The Journal of Clinical Psychiatry* 68 (Suppl 8): 4–10.

Sackeim, Harold A., Scott T. Aaronson, Linda L. Carpenter, Todd M. Hutton, Miriam Mina, Kenneth Pages, Sarah Verdoliva, and W. Scott West. 2020. "Clinical Outcomes in a Large Registry of Patients with Major Depressive Disorder Treated with Transcranial Magnetic Stimulation." *Journal of Affective Disorders* 277: 65–74. https://doi.org/10.1016/j.jad.2020.08.005.

Sanchez, Connie, Elin H. Reines, and Stuart A. Montgomery. 2014. "A Comparative Review of Escitalopram, Paroxetine, and Sertraline." *International Clinical Psychopharmacology* 29 (4): 185–96. https://doi.org/10.1097/yic.0000000000000023.

Sansone, Randy A., and Lori A. Sansone. 2014. "Serotonin Norepinephrine Reuptake Inhibitors: A Pharmacological Comparison." *Innovations in Clinical Neuroscience* 11 (3–4): 37–42.

Saveanu, Radu, Amit Etkin, Anne-Marie Duchemin, Andrea Goldstein-Piekarski, Anett Gyurak, Charles Debattista, Alan F. Schatzberg, et al. 2015. "The International Study to Predict Optimized Treatment in Depression (iSPOT-D): Outcomes from the Acute Phase of Antidepressant Treatment." *Journal of Psychiatric Research* 61 (World Psychiatry 8 3 2009): 1–12. https://doi.org/10.1016/j.j.psychires.2014.12.018.

Schomer, Donald L., and Fernando H. Lopes da Silva. 2011. *Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. 6th ed. Lippincott Williams & Wilkins.

Schür, Remmelt R., Dick Schijven, Marco P. Boks, Bart P. F. Rutten, Murray B. Stein, Jan H. Veldink, Marian Joëls, et al. 2019. "The Effect of Genetic Vulnerability and Military Deployment on the Development of Post-Traumatic Stress Disorder and Depressive Symptoms." *European Neuropsychopharmacology* 29 (3): 405–15. https://doi.org/10.1016/j.euroneuro.2018.12.009.

Silva, Fernando Lopes da. 1991. "Neural Mechanisms Underlying Brain Waves: From Neural Membranes to Networks." *Electroencephalography and Clinical Neurophysiology* 79 (2): 81–93. https://doi.org/10.1016/0013-4694(91)90044-5.

Silva, Fernando Lopes da. 2013. "EEG and MEG: Relevance to Neuroscience." *Neuron* 80 (5): 1112–28. https://doi.org/10.1016/j.neuron.2013.10.017.

Simon, Gregory E. 2002. "Evidence Review: Efficacy and Effectiveness of Antidepressant Treatment in Primary Care." *General Hospital Psychiatry* 24 (4): 213–24. https://doi.org/10.1016/s0163-8343(02)00198-6.

Smit, D. J. A., D. Posthuma, D. I. Boomsma, and E. J. C. de Geus. 2005. "Heritability of Background EEG across the Power Spectrum." *Psychophysiology* 42 (6): 691–97. https://doi.org/10.1111/j.1469-8986.2005.00352.x.

Smoller, Jordan W., Nicholas Craddock, Kenneth Kendler, Phil Hyoun Lee, Benjamin M. Neale, John I. Nurnberger, Stephan Ripke, Susan Santangelo, and Patrick F. Sullivan. 2013. "Identification of Risk Loci with Shared Effects on Five Major Psychiatric Disorders: A Genome-Wide Analysis." *The Lancet* 381 (9875): 1371–79. https://doi.org/10.1016/s0140-6736(12)62129-1.

Stewart, Jennifer L., David N. Towers, James A. Coan, and John J.B. Allen. 2011. "The Oft-Neglected Role of Parietal EEG Asymmetry and Risk for Major Depressive Disorder." *Psychophysiology* 48 (1): 82–95. https://doi.org/10.1111/j.1469-8986.2010.01035.x.

Straten, Annemieke van, Jacqueline J. Hill, David A. Richards, and Pim Cuijpers. 2014. "Stepped Care Treatment Delivery for Depression: A Systematic Review and Meta-Analysis." *Psychological Medicine* 45 (2): 231–46. https://doi.org/10.1017/s0033291714000701.

Straten, Annemieke van, Wike Seekles, Nelleke J. van 't Veer-Tazelaar, Aartjan T. F. Beekman, and Pim Cuijpers. 2010. "Stepped Care for Depression in Primary Care: What Should Be Offered and How?" *Medical Journal of Australia* 192 (S11): S36–39. https://doi.org/10.5694/j.1326-5377.2010.tb03691.x.

Surís, Alina, Ryan Holliday, and Carol S. North. 2016. "The Evolution of the Classification of Psychiatric Disorders." *Behavioral Sciences* 6 (1): 5. https://doi.org/10.3390/bs6010005.

Swanson, James M., Marcel Kinsbourne, Joel Nigg, Bruce Lanphear, Gerry A. Stefana-

tos, Nora Volkow, Eric Taylor, B. J. Casey, F. Xavier Castellanos, and Pathik D. Wadhwa. 2007. "Etiologic Subtypes of Attention-Deficit/Hyperactivity Disorder: Brain Imaging, Molecular Genetic and Environmental Factors and the Dopamine Hypothesis." *Neuropsychology Review* 17 (1): 39–59. https://doi.org/10.1007/s11065-007-9019-9.

Tansey, Katherine E., Michel Guipponi, Nader Perroud, Guido Bondolfi, Enrico Domenici, David Evans, Stephanie K. Hall, et al. 2012. "Genetic Predictors of Response to Serotonergic and Noradrenergic Antidepressants in Major Depressive Disorder: A Genome-Wide Analysis of Individual-Level Data and a Meta-Analysis." *PLoS Medicine* 9 (10): e1001326. https://doi.org/10.1371/journal.pmed.1001326.

Tatsumia, Masahiko, Karen Groshan, Randy D. Blakely, and Elliott Richelson. 1997. "Pharmacological Profile of Antidepressants and Related Compounds at Human Monoamine Transporters." *European Journal of Pharmacology* 340 (2–3): 249–58. https://doi.org/10.1016/s0014-2999(97)01393-9.

Taylor, Joseph J., Christopher Lin, Daniel Talmasov, Michael A. Ferguson, Frederic L. W. V. J. Schaper, Jing Jiang, Madeleine Goodkind, et al. 2023. "A Transdiagnostic Network for Psychiatric Illness Derived from Atrophy and Lesions." *Nature Human Behaviour*, 1–10. https://doi.org/10.1038/s41562-022-01501-9.

Tenke, Craig E., Jürgen Kayser, Carlye G. Manna, Shiva Fekri, Christopher J. Kroppmann, Jennifer D. Schaller, Daniel M. Alschuler, Jonathan W. Stewart, Patrick J. McGrath, and Gerard E. Bruder. 2011. "Current Source Density Measures of Electroencephalographic Alpha Predict Antidepressant Treatment Response." B*io logical Psychiatry* 70 (4): 388–94. https://doi.org/10.1016/j.biopsych.2011.02.016.

Tenke, Craig E., Jürgen Kayser, Jorge E. Alvarenga, Karen S. Abraham, Virginia Warner, Ardesheer Talati, Myrna M. Weissman, and Gerard E. Bruder. 2018. "Temporal Stability of Posterior EEG Alpha over Twelve Years." *Clinical Neurophysiology* 129 (7): 1410–17. https://doi.org/10.1016/j.clinph.2018.03.037.

Tjepkema-Cloostermans, Marleen C., Rafael C.V. de Carvalho, and Michel J.A.M. van Putten. 2018. "Deep Learning for Detection of Focal Epileptiform Discharges from Scalp EEG Recordings." *Clinical Neurophysiology* 129 (10): 2191–96. https://doi.org/10.1016/j.clinph.2018.06.024.

Trull, Timothy J, Kenneth J. Sher, Christa Minks-Brown, Jennifer Durbin, and Rachel Burr. 2000. "Borderline Personality Disorder and Substance Use Disorders A Review and Integration." *Clinical Psychology Review* 20 (2): 235–53. https://doi.org/10.1016/s0272-7358(99)00028-8.

Turner, R., Alastair Howseman, Geraint E. Rees, Oliver Josephs, and Karl Friston. 1998. "Functional Magnetic Resonance Imaging of the Human Brain: Data Acquisition and Analysis." *Experimental Brain Research* 123 (1–2): 5–12. https://doi.org/10.1007/s002210050538.

Uffelmann, Emil, Qin Qin Huang, Nchangwi Syntia Munung, Jantina de Vries, Yukinori Okada, Alicia R. Martin, Hilary C. Martin, Tuuli Lappalainen, and Danielle Posthuma. 2021. "Genome-Wide Association Studies." *Nature Reviews Methods Primers* 1 (1): 59. https://doi.org/10.1038/s43586-021-00056-9.

Uher, Rudolf, Nader Perroud, Mandy Y. M. Ng, Joanna Hauser, Neven Henigsberg, Wolfgang Maier, Ole Mors, et al. 2010. "Genome-Wide Pharmacogenetics of Antidepressant Response in the GENDEP Project." *American Journal of Psychiatry* 167 (5): 555–64. https://doi.org/10.1176/appi.ajp.2009.09070932.

Ulke, Christine, Craig E. Tenke, Jürgen Kayser, Christian Sander, Daniel Böttger, Lidia

Y. X. Wong, Jorge E. Alvarenga, et al. 2018. "Resting EEG Measures of Brain Arousal in a Multisite Study of Major Depression." *Clinical EEG and Neuroscience* 50 (1): 3–12. https://doi.org/10.1177/1550059418795578.

Ulrich, G., E. Renfordt, and K. Frick. 1986. "The Topographical Distribution of Alpha-Activity in the Resting EEG of Endogenous-Depressive In-Patients with and without Clinical Response to Pharmacotherapy." *Pharmacopsychiatry* 19 (04): 272–73. https://doi.org/10.1055/s-2007-1017230.

Umemoto, Akina, Lidia Y. X. Panier, Sally L. Cole, Jürgen Kayser, Diego A. Pizzagalli, and Randy P. Auerbach. 2021. "Resting Posterior Alpha Power and Adolescent Major Depressive Disorder." *Journal of Psychiatric Research* 141: 233–40. https://doi.org/10.1016/j.jpsychires.2021.07.003.

Vieta, Eduard. 2015. "Personalized Medicine Applied to Mental Health: Precision Psychiatry." *Revista de Psiquiatría y Salud Mental* (English Edition) 8 (3): 117–18. https://doi.org/10.1016/j.rpsmen.2015.03.007.

Vinne, Nikita van der, Madelon A. Vollebregt, A. John Rush, Michiel Eebes, Michel J.A.M. van Putten, and Martijn Arns. 2021. "EEG Biomarker Informed Prescription of Antidepressants in MDD: A Feasibility Trial." *European Neuropsychopharmacology* 44: 14–22. https://doi.org/10.1016/j.euroneuro.2020.12.005.

Vinne, Nikita van der, Madelon A. Vollebregt, Michel J. A. M. van Putten, and Martijn Arns. 2017. "Frontal Alpha Asymmetry as a Diagnostic Marker in Depression: Fact or Fiction? A Meta-Analysis." *NeuroImage: Clinical* 16 (Biol. Psychol. 67 1–2 2004): 79–87. https://doi.org/10.1016/j.nicl.2017.07.006.

Vinne, Nikita van der, Madelon A. Vollebregt, Michel J.A.M. van Putten, and Martijn Arns. 2019. "Stability of Frontal Alpha Asymmetry in Depressed Patients during Antidepressant Treatment." *Neuroimage Clin*, 24: 102056. https://doi.org/10.1016/j.nicl.2019.102056.

Vinne, Nikita van der, Madelon A. Vollebregt, Nash N. Boutros, Kamran Fallahpour, Michel J. A. M. van Putten, and Martijn Arns. 2019. "Normalization of EEG in Depression after Antidepressant Treatment with Sertraline? A Preliminary Report." *Journal of Affective Disorders*, 259: 67–72. https://doi.org/10.1016/j.jad.2019.08.016.

Voetterl, Helena T. S., Alexander T. Sack, Sebastian Olbrich, Sven Stuiver, Renee Rouwhorst, Amourie Prentice, Diego A. Pizzagalli, et al. 2023. "Alpha Peak Frequency-Based Brainmarker-I as a Method to Stratify to Pharmacotherapy and Brain Stimulation Treatments in Depression." *Nature Mental Health*, 1–10. https://doi.org/10.1038/s44220-023-00160-7.

Voetterl, Helena, Guido van Wingen, Giorgia Michelini, Kristi R. Griffiths, Evian Gordon, Roger DeBeus, Mayuresh S. Korgaonkar, et al. 2022. "Brainmarker-I Differentially Predicts Remission to Various Attention-Deficit/Hyperactivity Disorder Treatments: A Blinded Discovery, Transfer and Validation Study." *Biological Psychiatry*: *Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2022.02.007.

Voigt, Jeffrey, Linda Carpenter, and Andrew Leuchter. 2019. "A Systematic Literature Review of the Clinical Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) in Non-Treatment Resistant Patients with Major Depressive Disorder." *BMC Psychiatry* 19 (1): 13. https://doi.org/10.1186/s12888-018-1989-z.

Wackermann, J. 1996. "Beyond Mapping: Estimating Complexity of Multichannel EEG Recordings." *Acta Neurobiologiae Experimentalis* 56 (1): 197–208.

Ward, Joey, Nicholas Graham, Rona J. Strawbridge, Amy Ferguson, Gregory Jenkins,

Wenan Chen, Karen Hodgson, et al. 2018. "Polygenic Risk Scores for Major Depressive Disorder and Neuroticism as Predictors of Antidepressant Response: Meta-Analysis of Three Treatment Cohorts." *PLoS One* 13 (9): e0203896. https://doi.org/10.1371/journal.pone.0203896.

Wassermann, Eric M., and Sarah H. Lisanby. 2001. "Therapeutic Application of Repetitive Transcranial Magnetic Stimulation: A Review." *Clinical Neurophysiology* 112 (8): 1367–77. https://doi.org/10.1016/s1388-2457(01)00585-5.

Weiner, Luisa, Nader Perroud, and Sébastien Weibel. 2019. "Attention Deficit Hyperactivity Disorder And Borderline Personality Disorder In Adults: A Review Of Their Links And Risks." *Neuropsychiatric Disease and Treatment* 15: 3115–29. https://doi.org/10.2147/ndt.s192871.

Widge, Alik S., M. Taha Bilge, Rebecca Montana, Weilynn Chang, Carolyn I. Rodriguez, Thilo Deckersbach, Linda L. Carpenter, Ned H. Kalin, and Charles B. Nemeroff. 2019. "Electroencephalographic Biomarkers for Treatment Response Prediction in Major Depressive Illness: A Meta-Analysis." *The American journal of psychiatry*, 176 (1): 44–56. https://doi.org/10.1176/appi.ajp.2018.17121358.

Williams, Leanne M., A. John. Rush, Stephen H. Koslow, Stephen R. Wisniewski, Nicholas J. Cooper, Charles B. Nemeroff, Alan F. Schatzberg, and Evian Gordon. 2011. "International Study to Predict Optimized Treatment for Depression (iSPOT-D), a Randomized Clinical Trial: Rationale and Protocol." *Trials* 12: 1–17. https://doi.org/10.1186/1745-6215-12-4.

Wisor, Jonathan P., Seiji Nishino, Ichiro Sora, George H. Uhl, Emmanuel Mignot, and Dale M. Edgar. 2001. "Dopaminergic Role in Stimulant-Induced Wakefulness." *The Journal of Neuroscience* 21 (5): 1787–94. https://doi.org/10.1523/jneurosci.21-05-01787.2001.

World Health Organization. 2017. "Depression and Other Common Mental Disorders: Global Health Estimates." Geneva. License: CC BY-NC-SA 3.0 IGO.

Wray, Naomi R., Tian Lin, Jehannine Austin, John J. McGrath, Ian B. Hickie, Graham K. Murray, and Peter M. Visscher. 2021. "From Basic Science to Clinical Application of Polygenic Risk Scores." *JAMA Psychiatry* 78 (1): 101–9. https://doi.org/10.1001/jamapsychiatry.2020.3049.

Wu, Wei, Yu Zhang, Jing Jiang, Molly V. Lucas, Gregory A. Fonzo, Camarin E. Rolle, Crystal Cooper, et al. 2020. "An Electroencephalographic Signature Predicts Antidepressant Response in Major Depression." *Nature Biotechnology* 38 (4): 439–47. https://doi.org/10.1038/s41587-019-0397-3.

Zhang, Yu, Wei Wu, Russell T. Toll, Sharon Naparstek, Adi Maron-Katz, Mallissa Watts, Joseph Gordon, et al. 2020. "Identification of Psychiatric Disorder Subtypes from Functional Connectivity Patterns in Resting-State Electroencephalography." *Nature Biomedical Engineering* 5 (4): 309–23. https://doi.org/10.1038/s41551-020-00614-8.

Zuddas, Alessandro, Bernadette Ancilletta, Pierandrea Muglia, and Carlo Cianchetti. 2000. "Attention-Deficit/Hyperactivity Disorder: A Neuropsychiatric Disorder with Childhood Onset." *European Journal of Paediatric Neurology* 4 (2): 53–62. https://doi.org/10.1053/ejpn.1999.0263.

ENGLISH SUMMARY

The current clinical practice in psychiatry relies on the Diagnostic and Statistical Manual of Mental Disorders for categorizing psychiatric disorders based on symptoms. However, this system has limitations, including inconsistent treatment responses and overlooking underlying mechanisms of mental dysfunction. Psychiatric disorders, like major depressive disorder (MDD) or attention deficit hyperactivity disorder (ADHD), are heterogenous and often co-occur with other psychiatric disorders, suggesting the need for more personalized approaches. Traditionally, treatment decisions follow a stepped-care model, but this may not adequately address the complexity of mental health conditions. Transdiagnostic psychiatry proposes a shift towards understanding common factors across disorders rather than rigid diagnostic categories, potentially simplifying treatment protocols and improving outcomes.

Transdiagnostic markers, based on objective measures (e.g. genetic variants or neuroimaging characteristics) can help understand the mechanisms underlying psychiatric conditions and aid in predicting treatment response. Moreover, deep learning, a subtype of artificial intelligence, holds promise in automating identification of markers

from large data.

This thesis aimed to identify transdiagnostic markers from electroencephalography (EEG) data, for predicting treatment response in MDD and ADHD. Hereby, we leveraged large and heterogeneous datasets to capture a broad range of EEG features. Utilizing a data-driven data-reduction method at source level activity, various independent EEG-derived functional brain networks were extracted. Polygenic association analysis was employed to select biologically feasible networks, potentially predictive of treatment outcomes. The results of the proof-of-concept study and follow-up study revealed respectively a slow wave network and posterior alpha network related to age, with sex-specific and medication-specific treatment predictive capabilities for MDD, demonstrating the stratification potential of this innovative approach.

The final study focused on the intersection between biology and neuropsychology, concentrating on objective measures for impulsivity and sleep within the Research Domain Criteria (RDoC) arousal/regulatory domain. Patients with poor impulse control exhibited heightened activity in a frontal beta network. Furthermore, we explored how sleep maintenance problems were related to impulse control on one hand, and to frontocentral EEG beta activity as a marker for hypoarousal on the other. Our findings indicated that spindling excessive beta (SEB) probability, a measure derived through deep learning, is a transdiagnostic state marker for hypoarousal caused by sleep maintenance problems, with concurrent poor impulse control (and is not necessarily a direct marker for impulsivity).

Furthermore, we discovered that frontocentral beta activity has treatment predictive capacities. Specifically, we found that SEB probability predicts treatment outcomes in MDD in a drug-specific manner, while beta power in frontocentral regions is predictive for treatment outcome in girls with ADHD. The results provided insights into the complex interplay among regulatory mechanisms governing sleep, arousal and affect.

In summary, the findings emphasize the potential of employing a network-based and RDoC approach in biomarker research. The integration of objective measures such as EEG, genetics, and sleep data, holds promise for future investigations into biomarkers predicting treatment outcomes. Although this thesis does not directly lead to immediate changes in psychiatric care, it represents a necessary first-step towards future advancements in scientific research on biomarkers. Overall, this doctoral thesis underscores a shift towards more targeted approaches compared to current treatment paradigms, which ultimately may lead to a better understanding of psychiatric disorders and improved treatment outcomes.

NEDERLANDSE SAMENVATTING

De huidige klinische praktijk in de psychiatrie vertrouwt op de Diagnostic and Statistical Manual of Mental Disorders voor het categoriseren van psychiatrische stoornissen op basis van symptomen. Dit systeem heeft echter beperkingen, waaronder inconsistente behandeluitkomsten en het over het hoofd zien van onderliggende mechanismen van psychische disfunctie. Psychiatrische stoornissen, zoals een depressieve stoornis of aandachtstekortstoornis met hyperactiviteit (ADHD), zijn heterogene ziektebeelden en komen vaak samen voor met andere psychiatrische aandoeningen, wat wijst op de noodzaak van meer gepersonaliseerde benaderingen. Traditioneel volgen behandelbeslissingen een 'stepped-care-model', maar dit pakt de complexiteit van psychische aandoeningen mogelijk niet adequaat aan. Transdiagnostische psychiatrie stelt een verschuiving voor naar het begrijpen van gemeenschappelijke factoren tussen stoornissen in plaats van rigide diagnostische categorieën, wat de behandelprotocollen zou kunnen vereenvoudigen en de behandelresultaten zou kunnen verbeteren.

Transdiagnostische markers, gebaseerd op objectieve metingen (zoals genetische varianten of kenmerken op basis van neuroimaging),

kunnen helpen bij het begrijpen van mechanismen die ten grondslag liggen aan psychiatrische aandoeningen en bij het voorspellen van behandelrespons. Bovendien kan deep learning, een vorm van artificiële intelligentie, behulpzaam zijn bij het automatiseren van de identificatie van markers uit grote data.

Dit proefschrift had tot doel om transdiagnostische markers te identificeren in elektro-encefalografie (EEG) data, die behandelrespons bij depressie en ADHD kunnen voorspellen. Hierbij maakten we gebruik van grote en heterogene datasets, om zodoende een breed scala aan EEG-kenmerken te verkrijgen. Door gebruik te maken van een data-gedreven data-reductiemethode op bronniveau-activiteit werden verschillende onafhankelijke EEG-afgeleide functionele hersennetwerken geëxtraheerd. Polygene associatieanalyse werd gebruikt om netwerken te selecteren, die het meest waarschijnlijk samenhangen met biologische processen, en daarmee potentieel voorspellend zijn voor behandelresultaten. In de proof-of-conceptstudie en follow-upstudie werden respectievelijk een netwerk met langzame golfactiviteit en een posterieur alfa-netwerk (dat was gerelateerd aan leeftijd) geselecteerd. De netwerken hadden sekse-specifieke en medicijn-specifieke voorspellende capaciteiten voor de behandeluitkomst bij een depressieve stoornis, wat de stratificatiepotentie van deze innovatieve aanpak aantoont.

De laatste studie legde de focus op de intersectie tussen biologie en neuropsychologie, met de nadruk op objectieve metingen voor impulsiviteit en slaap binnen het arousal/regulatory domein, afkomstig van de Research Domain Criteria (RDoC). Patiënten met een slechte impulscontrole vertoonden verhoogde activiteit in een frontaal bèta-netwerk. Bovendien onderzochten we hoe doorslaapproblemen gerelateerd waren aan impulscontrole enerzijds, en aan frontocentrale EEG bèta-activiteit als marker voor hypoarousal anderzijds. De bevindingen lieten zien dat de waarschijnlijkheid van aanwezigheid van spindling excessive beta (SEB), een maat afgeleid door deep learning, een transdiagnostische marker is voor hypoarousal veroorzaakt door doorslaapproblemen, en gelijktijdig aanwezige slechte impulscontrole (en niet zozeer een directe indicator is voor impulsiviteit).

Frontocentrale bèta-activiteit heeft bovendien behandeluitkomst-voorspellende capaciteiten. Specifiek vonden we dat de SEB-waarschijnlijkheid de behandelresultaten voorspelt voor depressie op een medicatie-specifieke manier, terwijl bèta-activiteit in frontocentrale gebieden voorspellend is voor meisjes met ADHD. De resultaten leverden inzichten op in de complexe interactie tussen regulerende mechanismen die slaap, arousal en affect beheersen.

Samenvattend benadrukken de bevindingen het potentieel van het toepassen van een netwerk-gebaseerde en RDoC-benadering in biomarkeronderzoek. De integratie van objectieve maten, zoals EEG, genetica en slaapdata, biedt hoop voor toekomstige onderzoeken naar biomarkers die behandelsresultaten voorspellen. Hoewel dit proefschrift niet direct leidt tot veranderingen in de psychiatrische zorg, betreft het een noodzakelijke eerste stap naar toekomstige ontwikkelingen in wetenschappelijk onderzoek naar biomarkers. Al met al onderstreept dit proefschrift een verschuiving naar meer gerichte benaderingen in vergelijking met huidige behandelingsparadigma's, die uiteindelijk kunnen leiden tot een beter begrip van psychiatrische stoornissen en verbeterde behandelresultaten.

IMPACT PARAGRAPH

While the findings of this work do not directly translate to psychiatric care, this thesis represents a necessary first step forward in shifting from traditional psychiatry towards personalized care (tailoring treatments to each individual's unique neurobiological profile), highlighting an intermediate phase known as stratified psychiatry. In traditional psychiatry, diagnoses like depression typically rely on symptom clusters, which may not comprehensively represent the fundamental underlying mechanisms of mental disorders, given their heterogeneous symptomatology. However, treatment decisions often adhere to a one-size-fits-all approach informed by diagnosis due to the absence of biomarkers reliably predicting treatment outcomes for individual patients. Consequently, this approach yields varied treatment responses and lacks precision in therapeutic interventions.

Central to this thesis is the transition from these diagnostic boundaries to a transdiagnostic approach. Transdiagnostic biomarkers can facilitate in patient stratification, which involves subgrouping patients who are more susceptible to responding to one relative to another treatment, thus potentially improving treatment outcomes. This thesis offers a transdiagnostic framework for future research on biomarkers predicting treatment response.

Here, the focus was on uncovering common brain patterns through electroencephalography (EEG) across various psychiatric disorders. Therefore, objective ('ground-truth') measurements, including polygenic (risk) scores (PRS), actigraphy and continuous performance tasks, were associated to EEG networks and signatures to elucidate the underlying neurobiological mechanisms of treatment response. A novel methodology was introduced for understanding and predicting treatment outcomes in psychiatric disorders, aiming to identify transdiagnostic brain markers to improve treatment response and remission rates. To achieve this, a proof-of-concept "genetics-informed, data-driven data-reduction approach" was presented, where multiple functional brain networks were extracted from EEG data within large and heterogenous cohorts. Subsequently, association analysis with PRS for antidepressant response (the ground-truth)

was performed in order to select biologically meaningful networks that may have genetic underpinnings linked to treatment response. Hereby, the limitations of subjective measures and biases inherent in traditional classification systems were overcome. The approach's value was confirmed through two studies, the proof-of-concept study and follow-up study, both demonstrating the capability of the identified networks for treatment prediction.

Genome-wide association studies (GWAS) typically demand large sample sizes, often ranging from several thousand to tens of thousands of individuals, to achieve sufficient statistical power to find genetic variants associated with specific traits or diseases. In contrast, PRS calculation cumulates the weighted effects of numerous common genetic variants identified through GWAS. Thus, by utilizing ground-truth PRS data extracted from expansive GWAS datasets, we were able to detect biologically plausible networks, even when working with smaller yet still substantial sample sizes for EEG-PRS association analysis.

The age-related posterior alpha network, probably reflecting neurodevelopmental trait characteristics, is interesting as it represents a promising biomarker for stratification, due to its stability over time and predictive capacities for treatment outcomes in depression. Future research should focus on further investigation of this network, as it holds the potential to provide significant insights into the development of targeted interventions that may have long-term prognostic value for psychiatric disorders.

Exploring objective neuropsychological measurements in relation to an EEG signature in frontocentral brain regions, known as spindling excessive beta (SEB), has provided valuable insights into the relationship between SEB, impulse control, and sleep. Results emphasized the significance of addressing sleep maintenance problems in treatment planning for all psychiatric patients. Additionally, it has become evident that frontocentral beta activity holds potential as a transdiagnostic brain marker for predicting treatment outcomes across various psychiatric disorders.

Furthermore, the development of a deep learning algorithm for the automatic detection of SEB presents a promising opportunity to streamline the detection process, alleviating the workload for clinicians and researchers, and facilitating large-scale studies on objectively determined SEB.

At last, our findings notably elucidated sex-specific effects, highlighting the importance of conducting research separately for men and women while considering diverse medications or treatment protocols. Additionally, medication-specific effects emerged not only for treatments with distinct modes of action, but also for medications presumed to be largely comparable, like the selective serotonergic reuptake inhibitors escitalopram and sertraline. Accounting for these potential differential effects in analyses on treatment prediction can pave the way for more tailored and effective interventions.

Looking ahead, I envision stratified psychiatry as a crucial transitional phase toward a more precise and personalized approach. Recognizing the necessity of biomarkers for this objective, I propose shifting away from the current diagnostic boundaries and embracing a research focus on a transdiagnostic approach as introduced in this thesis, which is grounded in objective measures such as genetics. However, it is essential to acknowledge the challenges ahead. Biomarker research in psychiatry faces many obstacles, necessitating collaboration across multiple clinics, large-scale data collection, validation in independent samples, and implementation studies to confirm their clinical utility, enhance predictive accuracy, and ultimately realize their full clinical potential.

Transdiagnostic biomarkers for stratification, when integrated into clinical care, can help clinicians in selecting treatments that are most likely to be effective for a particular patient, which could minimize the trial-and-error process associated with psychiatric treatments and leading to quicker symptom relief and remission. Nevertheless, clinical observation remains a fundamental aspect of psychiatric practice. While biomarkers can guide treatment decisions, they may not capture the full spectrum of an individual's presentation. Clinical observation enables clinicians to see nuances in psychiatric symp-

toms that biomarkers may overlook, and to incorporate other factors, such as social and environmental influences, into the treatment plan to enhance overall well-being.

In summary, this doctoral thesis offers a transdiagnostic framework for future research focused on stratified psychiatry and implementation studies, with the potential to revolutionize our understanding and treatment of psychiatric disorders.

CURRICULUM VITAE

Hannah Meijs was born on the 1st of August, 1990, in Maastricht, The Netherlands. She commenced her academic education at Maastricht University, resulting in the attainment of her Master's degree in Medicine in 2015. Following this, she practiced as a medical doctor for several years in the Netherlands and a half year in Paramaribo, Suriname. Subsequently, in September 2018, she started her psychiatry residency at GGNet, a mental health care institution, located in the Eastern Netherlands, including a one-year external research internship at University Medical Center (UMC) Utrecht in 2019 and an external clinical internship (outpatient clinic neuromodulation) at Radboudumc Nijmegen in 2023. During her research internship at UMC Utrecht, she focused on EEG and genetics under the guidance of Jurjen Luykx. It was during this time that she crossed paths with Martijn Arns. From September 2020, she transitioned into a PhD program at Brainclinics Research Institute in collaboration with Maastricht University, with Alexander Sack as her supervisor and Martijn and Jurjen serving as co-supervisors, resulting in the completion of this thesis.

During her time as a PhD student, Hannah attended international conferences, showcasing her work through poster presentations. Additionally, she delivered an oral presentation at the Voorjaarscongres of the Nederlandse Vereniging voor Psychiatrie (NVvP) in March 2023. While combining her research with her clinical duties as a psychiatry resident, Hannah has concluded her psychiatry residency in April 2024.

Hannah Meijs is geboren op 1 augustus 1990 in Maastricht, Nederland. Ze begon haar academische opleiding aan de Universiteit Maastricht, wat resulteerde in het behalen van haar masterdiploma Geneeskunde in 2015. Hierna werkte ze als arts enkele jaren in Nederland en een half jaar in Paramaribo, Suriname. Vervolgens begon ze in september 2018 als arts in opleiding tot psychiater bij GGNet, een instelling voor geestelijke gezondheidszorg in Oost-Nederland, waarbij ze een externe onderzoeksstage van een jaar deed aan het Univer-

sitair Medisch Centrum (UMC) Utrecht in 2019 en een externe klinische stage (polikliniek neuromodulatie) bij Radboudumc Nijmegen in 2023. Tijdens haar onderzoeksstage aan het UMC Utrecht richtte ze zich op EEG en genetica onder begeleiding van Jurjen Luykx. Het was in deze periode dat ze in contact kwam met Martijn Arns. Vanaf september 2020 maakte ze de overstap naar een PhD-programma bij Brainclinics Research Institute in samenwerking met de Universiteit Maastricht, met Alexander Sack als haar promotor en Martijn en Jurjen als copromotors, wat resulteerde in de voltooiing van dit proefschrift.

Gedurende haar tijd als PhD-student nam Hannah deel aan internationale congressen, waar ze haar werk presenteerde via posterpresentaties. Daarnaast gaf ze een mondelinge presentatie op het Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie (NVvP) in maart 2023. Terwijl Hannah haar onderzoek combineerde met haar klinische verplichtingen als arts in opleiding, heeft ze haar opleiding tot psychiater afgerond in april 2024.

LIST OF PUBLICATIONS

PUBLISHED

Kool, Lindy, Bob Oranje, Hannah Meijs, Bieke De Wilde, Jan Van Hecke, Peter Niemegeers, and Jurjen J Luykx. 2022. "Event-Related Potentials and Use of Psychotropic Medication in Major Psychiatric Disorders." *Psychiatry Research* 314: 114637. https://doi.org/10.1016/j.psychres.2022.114637.

Meijs, Hannah, Amourie Prentice, Bochao D. Lin, Bieke De Wilde, Jan Van Hecke, Peter Niemegeers, Kristel van Eijk, Jurjen J. Luykx, and Martijn Arns. 2022. "A Polygenic-Informed Approach to a Predictive EEG Signature Empowers Antidepressant Treatment Prediction: A Proof-of-Concept Study." E*uropean Neuropsychopharmacology* 62: 49–60. https://doi.org/10.1016/j.euroneuro.2022.07.006.

Meijs, Hannah, Helena Voetterl, Alexander T. Sack, Hanneke Dijk van, Bieke De Wilde, Jan Van Hecke, Peter Niemegeers, Evian Gordon, Jurjen J. Luykx, and Martijn Arns. 2024. "A Posterior-Alpha Ageing Network Is Differentially Associated with Antidepressant Effects of Venlafaxine and RTMS." *European Neuropsychopharmacology* 79: 7–16. https://doi.org/10.1016/j.euroneuro.2023.11.002.

Zandstra, Melissa G., Hannah Meijs, Metten Somers, Cornelis J. Stam, Bieke de Wilde, Jan van Hecke, Peter Niemegeers, Jurjen J. Luykx, and Edwin van Dellen. 2023. "Associations between Psychotropic Drugs and RsEEG Connectivity and Network Characteristics: A Cross-Sectional Study in Hospital-Admitted Psychiatric Patients." *Frontiers in Neuroscience* 17: 1176825. https://doi.org/10.3389/fnins.2023.1176825.

UNDER REVISION

Meijs, Hannah, Jurjen J. Luykx, Nikita van der Vinne, Rien Breteler, Evian Gordon, Alexander T. Sack, Hanneke van Dijk, Martijn Arns. A deep learning derived transdiagnostic EEG signature indexing hypoarousal and impulse control: Implications for treatment prediction in ADHD and MDD. [*Under review*]

CONFERENCE CONTRIBUTIONS AND OTHER PRESENTATIONS

ORAL PRESENTATIONS

EEG-component die samenhangt met polygene score voorspelt behandeluitkomst depressie, *Voorjaarscongres NVvP*, 30 maart 2023.

POSTER PRESENTATIONS

A polygenic-informed approach to a predictive EEG signature empowers antidepressant treatment prediction, *4th International Brain Stimulation Conference*, December 2021. For abstract see: *Brain Stimulation* 2021;14(6):P1694-1695.

Investigating EEG biomarker specificity to combined rTMS with psychotherapy: Psychotherapy, rTMS or sham? A blinded prediction study, *4th International Brain Stimulation Conference*, December 2021. For abstract see: *Brain Stimulation* 2021;14(6):P1601.

A posterior-alpha ageing network is differentially associated with antidepressant effects of venlafaxine and rTMS, *2nd BeNe Brain Stimulation Congress*, November 2023.

DANKWOORD

Vanzelfsprekend zijn er talloze mensen die hebben bijgedragen aan de totstandkoming van dit proefschrift, en ik wil hen graag hiervoor bedanken.

Allereerst mijn toenmalige opleider en copromotor Jurjen Luykx, die me heeft geïntroduceerd in de wereld van onderzoek op een moment dat ik twijfelde of een carrière als psychiater wel bij me paste. Jurjen, onder jouw enthousiasme en begeleiding in Utrecht heb ik niet alleen veel geleerd over onderzoek doen, maar heb ik ook hernieuwde motivatie gevonden om mijn weg te vervolgen als arts in opleiding. Je hebt me bovendien het vertrouwen en mogelijkheden gegeven om mijn opleiding te kunnen combineren met onderzoek.

Zonder het geloof en de steun van mijn andere copromotor Martijn Arns zou het echter niet mogelijk zijn geweest om mijn onderzoeksstage een vervolg te geven in de vorm van een promotietraject. Martijn, bedankt voor de kans die ik heb gekregen om deel uit te maken van het onderzoeksteam in Nijmegen en voor de ontzettend leerzame en leuke tijd die ik aldaar heb gehad. Je was altijd beschikbaar voor vragen of overleg en je hebt mij geleerd om op een andere wijze te denken. Je enthousiasme werkt bovendien aanstekelijk.

Graag wil ik ook mijn collega's van zowel UMC Utrecht als Brainclinics Nijmegen bedanken. Allereerst Edwin van Dellen, wiens toewijding en bijdrage aan het EEG-onderzoek erg waardevol waren. Ik heb hier veel van geleerd en mede daardoor de eerste stappen kunnen zetten die uiteindelijk tot dit proefschrift hebben geleid. Kristel en Bas, ook jullie wil ik bedanken voor de fijne samenwerking. Jullie uitleg en hulp met de genetische data waren onmisbaar. Daarnaast wil ik Melissa bedanken voor het oppakken van een deel van mijn onderzoek dat ik in Utrecht heb gedaan en voor het leveren van een mooie paper.

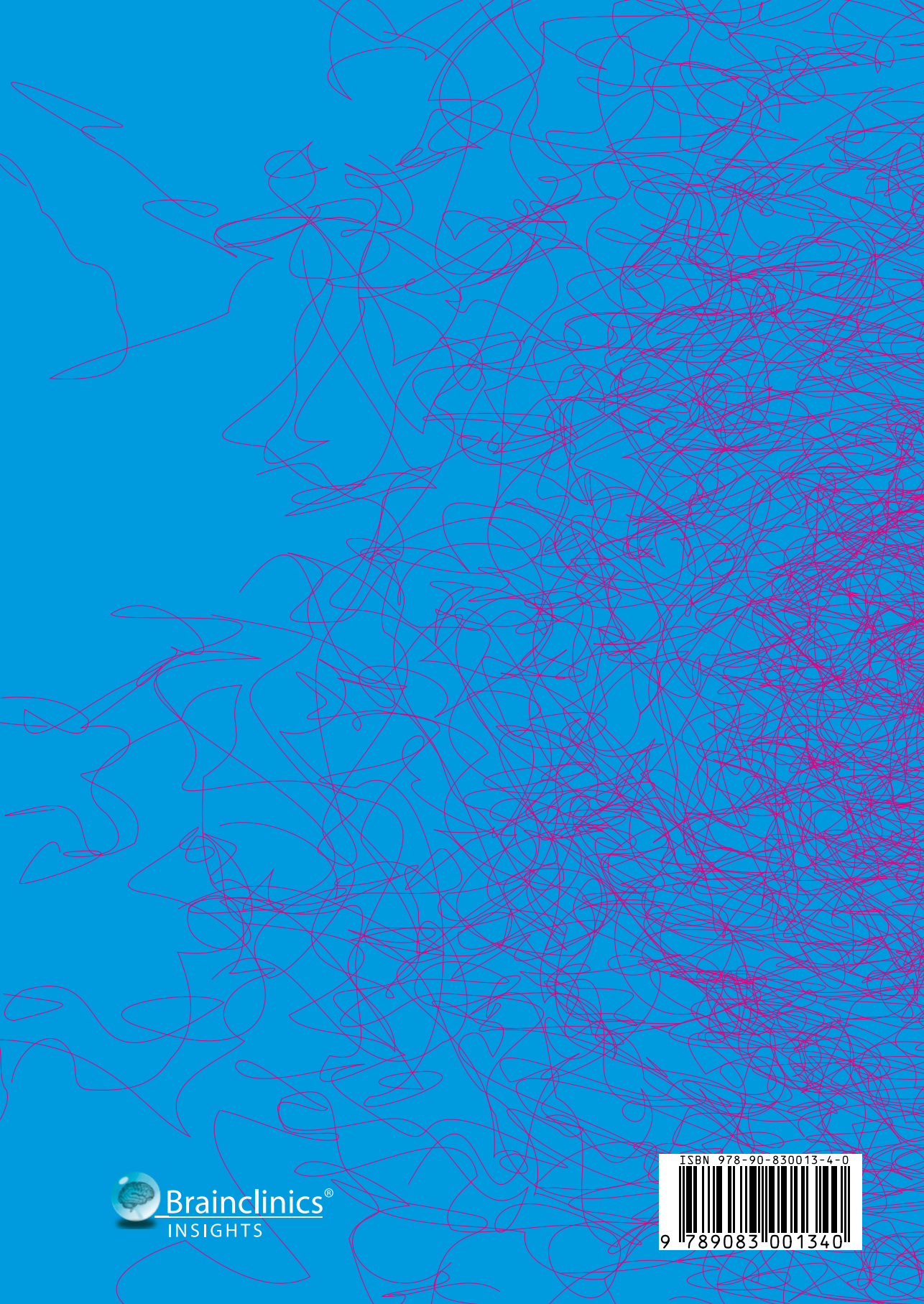
Van het Brainclinics team wil ik Hanneke bedanken voor haar nuttige input en feedback, en hulp met deep learning. En dan Mark, jouw bijdrage heeft mijn papers en proefschrift prachtig vormge-

geven. Samen met Hanneke vorm je een stabiele factor in het Brainclinics team en met jullie viel er altijd wat te lachen. Tot slot wil ik Helena, Eva, Lauren, Amourie, Nikita en andere collega's die ik maar kort gekend heb bedanken voor de prettige samenwerking en vooral ook de gezelligheid. Het congres in Charleston en de aansluitende roadtrip naar Miami zal ik niet gauw vergeten.

Dan wil ik me nog richten tot mijn promotor, Alexander Sack. Hoewel we elkaar weinig hebben gezien en gesproken, heb ik de samenwerking als prettig ervaren en jouw inzichten en begeleiding waardeer ik enorm.

I also wish to extend my gratitude to all co-authors and individuals who have contributed in any capacity to the papers presented in this thesis. While I cannot express my thanks to each of you individually, please know that your contributions are immensely valued and appreciated!

Als laatste wil ik graag mijn thuisfront bedanken. De afgelopen jaren waren niet altijd gemakkelijk, aangezien werk, opleidingsverplichtingen en sport veel van mijn tijd in beslag namen. Hierdoor bleef er bovendien (te) weinig tijd over voor een sociaal leven en was ik zelden in het zuiden van het land te vinden. Ik hoop dat dit nu verandert en ik weer meer tijd kan doorbrengen met familie en vrienden. Dank voor jullie steun!



ISBN 978-90-830013-4-0

Brainclinics®
INSIGHTS