A polygenic-informed approach to a predictive EEG signature empowers stratified antidepressant treatment

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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 differential antidepressant treatment response. Using a polygenic-informed electroencephalography (EEG) data-driven, data-reduction approach, we identify a functional brain network in a large cohort of predominantly psychiatric patients (N=1,123), and discover that this network is sex-specifically associated with polygenic liability to psychiatric illness. Subsequently, we demonstrate the utility of this network in predicting response to repetitive transcranial magnetic stimulation (rTMS) and antidepressant medication in two independent datasets (N=196 and N=1,008). A stratification model aimed at stratifying patients to rTMS or sertraline based on only this EEG component yields improved remission rates varying from 22% to 39%. Overall, our findings highlight the power and utility of a combined polygenic and neurophysiological approach in the search for clinically-relevant biomarkers in psychiatric disorders.

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 (1, 2). Furthermore, genetic risk factors of MDD overlap with other psychiatric disorders (3). It is assumed that this multifactorial model for MDD underlies its heterogeneous symptomatology and variable treatment efficacy (4, 5).

In line with the biological heterogeneity of MDD that in turn may be related to 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 (6), but clinically-relevant and converging loci have remained elusive (7–14). For repetitive transcranial magnetic stimulation (rTMS) responsiveness, to our knowledge, only one GWAS at relatively limited power is available (15). Thus, antidepressant treatment outcome is likely a complex trait and explained by several loci of small effect (16), with recent evidence indeed suggesting that antidepressant response is polygenic (6). 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 (17). However, despite recent evidence showing the power of PRS of MDD for a range of MDD-related phenotypes (18), at present evidence for the out-of-sample value of polygenic risk approaches in the prediction of treatment outcome is limited (6, 19–22). 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 (23).

Electroencephalography (EEG) is a non-invasive neuroimaging technique to quantitatively analyze oscillatory brain activity of neurons with high temporal resolution (24). Several EEG patterns are heritable,

in particular characteristics within the alpha frequency band and EEG power across the power spectrum (25–28). Some studies have also demonstrated heritability for functional connectivity and ('small world') network organization parameters, which have been linked to pathological states of the brain (29–31). 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 (32–34), as well as rTMS outcome (35–38). Such studies have also demonstrated qualitative sex differences in topographic distribution of EEG activity and sex-specific predictors of treatment response of alpha asymmetry (33), EEG connectivity (39), and event-related potentials (40), and therefore we performed our analyses on men and women separately. Until recently, it was concluded that findings are insufficiently validated and replicated, and do not yet support the use of EEG for clinical decision making (41). However, two recent studies using machine-learning algorithms applied to resting-state EEG features identified predictive signatures for sertraline, a selective serotonin-reuptake inhibitor, that related differentially to rTMS response (42, 43). 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), aiming to increase initial treatment response, without the requirement to consider off-label prescriptions or simply 'withhold' treatment due to a biomarker predicting low likelihood of response (44).

Here, our aim was to predict treatment outcome in MDD based on an EEG signature using a polygenic-informed EEG data-driven, data-reduction approach: we used several PRSs to guide the selection of functional brain networks for subsequent response prediction, thus combining genetics with neurophysiology approaches. 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 of severely ill psychiatric patients and healthy controls. In a prior study, this fICA method was tested and validated (45, 46), and demonstrated to reliably identify the default mode network (DMN) and task-positive network (TP) in a sample of 1,397 subjects, replicated in an independent ADHD sample (45). Here, we show that two functional networks are significantly associated with polygenic liability to multiple common psychiatric disorders (PRS-cross disorder). Then, we discovered that only the strongest associated one is also associated with the PRS for MDD. This network was selected for subsequent translational analysis in two large independent datasets consisting of MDD patients, which demonstrated how this EEG signature is differentially associated with antidepressant treatment to rTMS and antidepressant medication. Finally, in stratification approaches we show that the prediction accuracy of antidepressant treatment remission increases, by stratifying patients to one of two treatments by this polygenic-informed EEG component.

Results

An overview of the baseline demographic characteristics and response and remission rates per dataset after EEG preprocessing can be found in Table 1. The analysis procedure that was performed in this study is visualized in Fig. 1.

Table 1. *Baseline characteristics*

<i>Baseline characteristics</i>	<i>Dataset 1: genetics</i>	<i>Dataset 2: rTMS</i>	<i>Dataset 3: medication</i>
Total number participants,	1,195	196	1,008
N included for statistical analysis	1,123#	186	535
Ratio male/female participants	617/506	93/93	245/290
Mean age (SD), years	40.3 (13.2)	43.3 (12.9)	38.5 (12.6)
Self-reporting questionnaire; mean baseline score (SD)	BDI-II; 31.1 (12.1)	BDI-II; 30.8 (9.8)	QIDS; 14.5 (3.7)
Remission and response rate (%)	N/A*	55.4; 66.1	35.3; 48.8

Abbreviations: BDI-II=Beck Inventory Index, second version; QIDS=Quick Inventory of Depressive Symptomatology.

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

#N=1,123 subjects included in EEG statistical analyses, with N=722 included in subsequent PRS analyses.

Discovery analysis identifies 58 components using LORETA-fICA

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 58.2 dimensions; hence the LORETA-fICA analysis was constrained to 58 components that explained 96.0% of the total variance in EEG power (see Fig. 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-processing and genetic quality control (QC; see Table S1 for all QC steps). PRS for cross-disorder (a combined case-control GWAS of several psychiatric disorders) correlated significantly with the individual loading on the following two components, after controlling for age and the first five genetic principal components (PCs): component 13 in women ($r=-0.207$, $R^2=4.3\%$, optimal $P_T<0.4$) at $p=0.0002$ and component 24 in men ($r=0.182$, $R^2=3.3\%$, optimal $P_T<0.5$) at $p=0.0004$. The PRS model fit was indicative of high polygenicity (see Fig. 2). This was followed up by a correlation analysis of EEG component 13 and 24 with three disease-specific PRSs (for MDD, schizophrenia and alcohol dependence; the three most common disorders in dataset 1), which revealed that only EEG component 13 in women correlated with PRS-MDD ($r=-0.182$, $R^2=3.3\%$, only $P_T<5.0\times 10^{-8}$) at $p=0.001$). An exploratory SNP analysis separately for men and women, revealed that for five variants the component loading was

significantly different between homozygotes or heterozygotes for the alternate allele compared to homozygotes for the reference allele (Table S2). Notably, the loading was significantly different in subjects homozygous for a *SGIP1* (SH3 domain GRB2 like endophilin interacting protein 1) variant (rs6656912) compared to homozygotes for the reference allele, which was more pronounced and in opposite direction in men (Cohen's d , $d=-0.435$; $p=0.007$) relative to women ($d=0.310$; $p=0.041$).

Fig. 3 shows EEG component 13, representing jointly deactivation and activation of neural activities coming from sets of regions that form functional spatial-spectral networks. Most prominent were frontal alpha power, mainly seen at the left dorsolateral prefrontal cortex (DLPFC), inversely associated with delta and theta power in the right anterior portion of the PFC and delta power seen at a region surrounding the left lateral sulcus, mainly including somatosensory-motor cortices. We will refer to this component as the prefrontal and sensorimotor (PF-SM) network.

The individual loadings on the PF-SM network as visualized in Fig. 3 (see Fig. S1 for distribution curves of loadings per dataset), did not correlate with baseline characteristics and a sensitivity analysis revealed that the displayed results cannot be explained by frontal alpha asymmetry, as earlier reported by Arns et al. (33) on the same data (see Tables S3 and S4).

Translation analyses in two independent treatment response datasets

The primary outcome for translational analysis (see Fig. 1: translation) was dimensional improvement of depressive symptoms using linear regression, based on self-report questionnaire scores at baseline and after rTMS (dataset 2) or medication treatment (dataset 3). All data were normally distributed. The secondary analysis was focused on categorical improvement: response (defined as $\geq 50\%$ reduction of baseline severity score) and remission (defined as a score of ≤ 12 on the Beck Depression Inventory II, BDI-II, or ≤ 5 on the Quick Inventory of Depressive Symptomatology, QIDS).

Relating the PRS-informed EEG component to rTMS outcome (dataset 2)

Of the 196 dataset-2 participants, data of 186 were usable (receiving rTMS 1 Hz right DLPFC or 10 Hz left DLPFC, clean EEG and all channels available).

First, linear regression analysis of Δ BDI-II on individual EEG component loading with age as covariate yielded an R^2 of 7.9% ($p=0.007$) in women, and R^2 of 8.0% ($p=0.005$) in men, and R^2 of respectively 6.7% ($p=0.009$) and 6.4% ($p=0.008$) when baseline BDI-II score was also added as covariate.

Second, to examine categorical outcomes, we performed an ANCOVA with EEG component loading as dependent variable and remission and sex as fixed factors, and age and baseline BDI-II score as covariates yielded a significant remission x sex interaction ($F(1,180)=9.304$; $p=0.003$). Repeating the analysis for men and women separately resulted in a main effect of remission for women ($d=-0.439$; $F(1,89)=7.792$; $p=0.006$) and men ($d=0.438$; $F(1,89)=7.304$; $p=0.008$), in opposite direction. Subsequently, we performed an ANCOVA with EEG component loading as dependent variable and response and sex as

fixed factors, and age as covariate, which yielded a significant response x sex interaction ($F(1,181)=6.871$; $p=0.010$). Repeating the analysis for men and women separately resulted in a main effect of response for men ($d=0.596$; $F(1,90)=9.747$; $p=0.002$), but no main effect for women.

A discriminant analysis revealed that the EEG component alone significantly predicted remission in both women (Wilk's Lambda, $\Lambda=0.955$; Chi-Square, $\chi^2=4.193$; $p=0.041$), and men ($\Lambda=0.953$; $\chi^2=4.361$; $p=0.037$). Prediction improved when age and baseline BDI-II were added to the model in women ($\Lambda=0.678$; $\chi^2=34.840$; $p<0.0001$) and men ($\Lambda=0.809$; $\chi^2=18.977$; $p=0.0003$). The ROC for this analysis (see Fig. 4) yielded an area under the curve (AUC) of 0.815 in women ($p<0.0001$; 95%-confidence interval, $CI=[0.725-0.905]$) and AUC of 0.744 in men ($p<0.0001$; 95%- $CI=[0.646-0.843]$). A discriminant analysis showed that the EEG component significantly predicted response in men ($\Lambda=0.919$; $\chi^2=7.639$; $p=0.006$), and including age to the model resulted in an improved prediction model ($\Lambda=0.845$; $\chi^2=15.167$; $p=0.0005$). The ROC for this model (see Fig. S2) yielded an area under the curve (AUC) of 0.735 ($p=0.0001$; 95%- $CI=[0.636-0.835]$).

To explore if abovementioned significant results were driven by one of the two rTMS protocols (1 Hz R-DLPFC vs. 10 Hz L-DLPFC rTMS) a sensitivity analysis was performed. For response, running the ANCOVAs as above, adding rTMS protocol as fixed factor, yielded a significant main effect for 10 Hz rTMS in men only ($d=0.963$; $F(1,34)=9.752$; $p=0.004$), but not for 1 Hz rTMS, albeit the effect was in the same direction ($d=0.295$). This indicates the effect on response –which was only found in men– was mostly attributable to 10 Hz rTMS, while for remission in both sexes, no significant interactions with rTMS protocol were found.

Relating the PRS-informed EEG component to antidepressant medication outcome (dataset 3)

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

First, linear regression analysis of $\Delta QIDS$ on individual EEG component loading with age as covariate yielded an R^2 of 3.1% ($p=0.015$) in all subjects (men and women together) receiving sertraline treatment, and R^2 of 2.4% ($p=0.019$) when baseline QIDS score was also added as covariate. No significant associations were found in subjects receiving escitalopram or venlafaxine. Second, to examine categorical outcomes within the sertraline treatment group, we performed an ANCOVA with EEG component loading as dependent variable and response and sex as fixed factors, and age as covariate yielded a significant main effect of response for sertraline ($d=-0.309$; $F(1,177)=4.316$; $p=0.039$), but no interaction with sex. ANCOVA with EEG component loading as dependent variable and remission and sex as fixed factors, and age and baseline QIDS score as covariates yielded no significant results, suggesting the increased network activity is predictive for sertraline response, but not remission.

A discriminant analysis resulted in a significant contribution of the EEG component to the prediction of sertraline response in women and men together ($\Lambda=0.977$, $\chi^2=4.250$, $p=0.039$), but not for remission. Running the same analysis resulted in significantly improved models for response adding age

($\Lambda=0.948$; $\chi^2=9.618$; $p=0.008$) and for remission adding age and baseline QIDS ($\Lambda=0.870$; $\chi^2=24.823$; $p<0.0001$). The AUC of the ROC analyses were 0.634 ($p=0.002$; 95%-CI=[0.554-0.714]) for response (see Fig. S2) and 0.712 for remission ($p<0.0001$; 95%-CI=[0.636-0.788]; see Fig. 4).

Stratification demonstrates likelihood of remission is increased when using the EEG component

The optimal network loading cut-off points were determined by calculating the maximum Youden index (J) of the three ROC curves for remission as presented in Fig. 4. Regarding rTMS, the maximum Youden's J was at loading 254 ($J=0.320$) in women, while it was -197 ($J=0.236$) in men; the maximum Youden's J was at loading -164 ($J=0.213$) in men and women who were prescribed sertraline. For stratification purposes, we chose the cut-offs points of the two highest Youden Indices, thereby simplifying application of the component (see Fig. 5). Stratifying patients based on these cut-off points (i.e. predicting remission or non-remission) resulted in significantly better within-subsample remission rates (i.e. PPV's) than expected based on the observed (non-stratified) remission rates: PPV=77% (improvement 39%; $\chi^2=10.126$; $p=0.002$) for rTMS in women, PPV=68% (improvement 22%; $\chi^2=5.099$; $p=0.036$) for rTMS in men, and PPV=45% (improvement 30%; $\chi^2=6.691$; $p=0.013$) for sertraline treatment (see Table S5). For women prescribed escitalopram or venlafaxine the remission rate was not significantly better, but stratification nevertheless resulted in an improved remission rate of 5.6%.

Discussion

Given psychological measures mapping poorly on neurobiology and cognizant of the scarce diagnostic and prognostic biomarkers in MDD (47–49), we have here taken a novel, genetics-informed approach to elucidate whether a polygenic-informed EEG signature may help predict differential antidepressant treatment response. 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 differentially associated with two evidence-based antidepressant treatments in independent datasets consisting of MDD patients.

Visualizing our functional network (Fig. 3), we found 1) prefrontal jointly left-sided alpha power (mainly DLPFC) that was inversely associated with right-sided slow delta and theta power (mainly in the anterior portion of the PFC); 2) slow delta power surrounding the left lateral sulcus, including the somatosensory-motor and auditory cortex; 3) asymmetrical alpha activity in the visual cortex. The individual strength of this PF-SM network was differentially associated with treatment outcomes to rTMS in a sex-specific manner, and to sertraline (similar for men and women), but no such associations for escitalopram or venlafaxine were detected. Several hypotheses might explain the predictive value of the PF-SM 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 (50). TMS applied to the PFC, however, results in transsynaptic activation of deeper areas such as the sgACC (51), and the frontal-vagal pathway (52). 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 PF-SM network in a cross-frequency manner. An organized neural circuit between the PFC and motor and somatosensory cortices has been described (53). Also, TMS induces anticorrelations between the DLPFC and medial prefrontal areas of the default mode network (54). Notably, the effect we detected was mostly driven by high frequency (10 Hz) stimulation at the left DLPFC, which was previously associated with a network synchronizing effect in the alpha frequency band (38). This protocol-specific effect was most predominantly found in men. Furthermore, while increasing PF-SM network activity was significantly related to improvement of depressive symptoms after rTMS in women, the reverse effect was found in men. These findings hint at different underlying mechanisms of action of TMS on neural activity in men relative to women, and are supported by previous studies reporting sex-specific differences in TMS response (55–57). On a SNP level, the PF-SM network loading was also different in subjects homozygous for the rs6656912 variant (*SGIP1*), compared to reference allele homozygotes, which was more pronounced and in opposite direction in men compared to women. *SGIP1* is expressed predominantly in the brain and encodes a protein required for the neuronal regulation of energy homeostasis (58). Recently, it was hypothesized that *SGIP1* may be involved in processes regulated by Wnt signaling, together with other protein interactors of Wntless (Wl, essential protein for the secretion of multiple Wnt proteins (59)) that are expressed in the brain, such as the dopamine transporter (60). Differences in Wnt signaling may partly underlie the reversed treatment outcomes found men and women. Further research is warranted to investigate these sex-specific mechanisms.

In both sexes, increased PF-SM network activity was antidepressant-specifically related to sertraline response, but not to escitalopram or venlafaxine. Sertraline, in contrast to the other two antidepressants, is also a synaptic dopamine reuptake inhibitor that increases extracellular levels of dopamine (61, 62). Potential involvement of dopamine in the PF-SM network is supported by the finding that rTMS of the left PFC can induce dopamine release in the striatum (63). Dopamine plays a prominent role in many functions that are impaired in MDD, such as execution of movement, executive cognitive functioning, and the ability to experience pleasure (64). Downregulation of the dopamine system, leading to dysfunction of neural circuits such as PFC-amygdala functional connectivity, has been implicated in the pathophysiology of MDD (65). Evidence also suggests involvement of dopaminergic systems in the modulation of sensorimotor gating (66), and indicates that MDD is characterized by dysregulation of sensorimotor processes that modulate depressive symptoms via fronto-limbic circuits (67, 68). Thus, the PF-SM network we uncover here may partly reflect a disrupted dopamine system, and therefore allows sertraline outcome prediction.

The predictive value of the network with regards to treatment outcome was tested in MDD patients receiving TMS treatment (dataset 2) and randomized antidepressant treatment (dataset 3). Primary analysis showed that increased network PF-SM strength was dimensionally associated with response to rTMS in women but to non-response in men, while it was non-sex-specifically associated with sertraline response. Secondary categorical analysis confirmed these results. Subsequent discriminant analysis suggested that the PF-SM network loading improved the basic model including the clinical variables age

and baseline severity symptom score for the prediction of remission and response. Lastly, based on the relative change on self-reporting questionnaires, two clinical cut-offs based on individual PF-SM network loadings were established. The results of the stratification indicated improved remission rates of 21.9% in men and 39.4% in women for rTMS, and of 30.2% in male and female patients prescribed sertraline. Rest-EEG recordings and subsequent calculation of PF-SM network loading in treatment-naïve MDD patients before treatment inception is likely relatively economical and non-invasive. Such an EEG signature may thus in future provide a useful construct for treatment stratification, thereby enhancing chances of initial remission (and response), thus limiting the relative inefficiency of the current stepped-care, 'trial-and-error' approach. For example, a clinician will prefer prescribing sertraline over escitalopram or venlafaxine to a female patient with PF-SM network loading >-197 , but will advise rTMS if the loading is even >254 to achieve best remission likelihood. In case of male patients, sertraline will also be first choice if the loading is >-197 , but rTMS if the loading is <-197 . Given that efficacy of antidepressant treatment in the general MDD population is moderate (69–71), and antidepressant discontinuation and switching rates are high (72–74), only slightly increased remission chances may reduce disease burden and duration.

External validation using three large, independent datasets is an important strength of this study. In addition, 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. On the other hand, the opposite effects for men and women for rTMS argue against a notion of none-specific effects. In addition, since all patients received psychotherapy concurrent with rTMS, we could not rule out that the EEG component was predictive for rTMS only. 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 stratification model we relied on the EEG signature, future studies should aim to further optimize stratification by also including other baseline variables, which are likely to further improve the clinical response.

In conclusion, we show for the first time how a genetics-informed data-driven, data-reduction approach identifies an EEG functional brain network that increases response prediction to two treatments in MDD. Our method highlights the clinical applicability of such an approach and sets the stage for future stratified psychiatry research.

Materials And Methods

Participants, 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 heterogeneous 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, restlessness that could interfere with the EEG, and inability to sit still. Only patients who were hospital-admitted for stabilization and/or treatment of a psychiatric disease (no further selection was made) were included to allow collection of a representative cohort of (severely ill) psychiatric patients. 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). 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 (75), to obtain a genetic homogeneous cohort, and PRSs were calculated conform standard procedures using PRSice2 (76).

Participants of the rTMS study, dataset 2

The second dataset was used for translational purposes and the evaluation of treatment effects. It consisted of 196 patients, diagnosed with non-psychotic MDD or dysthymia and BDI-II ≥ 14 at baseline, receiving protocolized rTMS treatment concurrent with psychotherapy. All participants provided written informed consent. Only participants receiving high-frequency TMS (10 Hz left dorsolateral prefrontal cortex, DLPFC) or low-frequency TMS (1 Hz right DLPFC) were included; participants receiving both 1 Hz and 10 Hz sequentially were excluded since this would make interpretation of results difficult. 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 (47, 77).

Participants of the medication study, dataset 3

The third 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), or 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 subsequently 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 (33, 78).

EEG recordings and preprocessing

Resting-state eyes closed EEG recordings (see Supplementary Materials and Methods) 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 of the Neuroscan NuAmps (Compumedics, Australia; dataset 2 and 3).

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 (79); 4) segmentation in 4-second epochs; and 4) artefact-rejection using an automatic procedure (criteria: maximal allowed difference of 150 μ V 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 (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 (80).

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 (46). In the third step, the spectral-spatial data of all subjects was concatenated, and ICA (see Supplementary Materials and Methods) was performed on this 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 (45, 46).

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 estimated from a measure related to Wackermann's Omega Complexity (81), indicating 58.2 dimensions, hence the LORETA-fICA analysis was constrained to 58 components explaining 96.0% of total EEG power variance.

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 loadings 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 loadings were obtained per network. These loadings were used in the statistical analysis.

Outcome measures

For component selection (discovery, Fig. 1), PRSs were examined in a two-stepped approach for association with the independent EEG components (dataset 1, see Statistics below). For the prediction analysis (translation, Fig. 1), the primary outcome was dimensional improvement of depressive symptoms, based on the BDI-II for rTMS sample (dataset 2) and the QIDS for iSPOT-D sample (dataset 3), which are both self-report questionnaires. To confirm the robustness of our findings, we then focused on categorical improvement, defined as remission or response. Self-reports were taken at intake and after treatment completion (on average at session 21 for rTMS and at week 8 for antidepressants). Remission (primary) was defined as a score of ≤ 12 on the BDI-II (82) (dataset 2) or ≤ 5 on the QIDS (83) (dataset 3), while response (secondary) was defined as $\geq 50\%$ reduction of baseline score.

Statistics

SPSS version 26 was used for statistical analyses. Effects sizes (ES) of significant main effects are reported as R^2 for continuous measures or as Cohen's d (d) for binary measures. Two-sided tests were performed for statistical significance testing.

A priori, analyses were stratified by sex, since previous iSPOT-D studies reported sex-specific predictors of treatment outcome (33, 39, 40, 78), and this would enable us to identify stratification biomarkers. Hence, sex was included as main factor or women and men were analyzed separately if the analysis could not accommodate sex as main factor, rather than handled as covariate since covariation can only resolve quantitative – not qualitative – sex differences. If no sex interaction was found or the effect for both sexes was the same direction, men and women were analyzed together.

First, a discovery analysis was performed to examine if there was an association between one or more fICA components and PRS-cross disorder (dataset 1) as this is the largest GWAS in psychiatry and given the heterogeneous psychiatric disorders in this dataset. To that end, a partial correlation analysis, controlling for age and the first five genetic ancestry principal components (PCs) on men and women separately, was run between all EEG fICA components loadings and 13 PRS p-value thresholds ($P_T=5.0 \times 10^{-8}$ to $P_T=1$) in order to choose the optimal P_T , which is unknown a priori (84). The Bonferroni-

corrected significance level was set to $\alpha = \frac{0.05/58 \text{ components}}{2 \text{ sexes (male + female)}} = 0.00043$ to reduce the likelihood of false positives and non-reproducibility of findings. Subsequently, a second association analysis with PRS for MDD (PRS-MDD), PRS for schizophrenia (PRS-SCZ) and PRS for

alcohol dependence (PRS-AD) was performed with those EEG components found to be significantly correlated with PRS-cross disorder, for disease-specific correlations. The Bonferroni-corrected significance level for this analysis was set at $\alpha = \frac{0.05/\text{number of components}}{3 \text{ PRSs (MDD + SCZ + AD)}}$ = 0.0083. DNA QC details, PRS calculation and references to the GWASs used for PRS generation may be found in Supplementary Materials and Methods.

Second, translational analyses were performed (dataset 2 and 3) to examine if the EEG component that showed Bonferroni-significant correlations with PRS-cross disorders and one additional PRS (i.e. PRS-MDD) was predictive of treatment outcome in datasets 2 and 3. 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 loading and absolute changes in BDI-II score (dataset 2) and QIDS score (dataset 3). The absolute change (Δ) was defined as the symptom severity score difference between baseline and at treatment completion. Therefore, for men and women separately, Δ BDI-II and Δ QIDS were regressed on EEG component loading, adding age and baseline self-report score as covariates. If significant associations were found, factorial ANCOVAs were run to investigate if the individual loadings on the EEG component were significantly different in remitting and responsive patients relative to non-remitters and non-responders, respectively. Remission/response and sex were added as fixed factors; age was added as covariate in all models. For remission, baseline BDI-II in dataset 2 and QIDS in dataset 3 (i.e. clinical score) were added as additional covariates since baseline severity was related to treatment remission, while response was not (47, 78).

Subsequently, to assess the predictive value of the EEG component, a discriminant analysis on treatment outcome was performed for datasets 2 and 3. 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 (47, 49). The baseline model consisted of the EEG component detected with our two-stepped PRS approach predicting outcome. Then we tested whether the model performance improved when age (for remission and response) and baseline severity (for remission only) were added as predictor(s). Also, a receiver operating characteristic (ROC) curve of both models was regressed on remission (primary) and response (secondary).

Finally, we attempted to make a construct, based on the data of both dataset 2 and dataset 3. The optimal network loading cut-off points of each sample were determined by calculating the maximum Youden Index (J), which measures the accuracy of a dichotomous diagnostic test, for the prediction of remission to increase effectiveness of EEG component (single predictor) as a potential biomarker. Based on these cut-offs, a stratification model was built to evaluate the clinical usefulness, by calculating the positive predictive value (PPV; i.e. subsample remission rate) in a cross tabulation, and improvement of remission if only subjects above or below one of the cut-offs were assigned to rTMS or sertraline treatment.

Declarations

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Figures

Discovery

Figure 1

The discovery analysis (dataset 1) using the LORETA-fICA method is shown left. Data for this method consisted of 6 a priori defined frequency bands and 6239 voxels (6x6239) per subject. This resulted in 58 independent cross-frequency spectral-spatial components. In a two-stepped PRS-association approach within a subsample, EEG component 13 (i.e. PF-SM network) was found to be robustly associated with 1) PRS-cross disorder (a combined case-control GWAS of several psychiatric disorders), and 2) PRS-MDD in women. This component was used for translational purposes in two independent datasets: MDD patients treated with rTMS and concurrent psychotherapy (dataset 2) and pharmacotherapy (dataset 3), which is

shown on the right. PF-SM network activity was differentially associated with rTMS response while similarly associated with sertraline response in men and women. Network activity was not associated with escitalopram or venlafaxine response.

Figure 2

The graphs show the explained variance (R^2 as %) on the left y-axis of the individual loading on EEG component 13 in women by PRS-CDG (polygenic risk score of cross-disorder; blue bars), and the corresponding p-value (presented as $-\log$; orange dot) on the right y-axis per p-value threshold (PT) on the y-axis. The Bonferroni-corrected significance level is also presented (α , grey dotted line). Note that, in general, the more lenient the PT 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.

Figure 3

Map of the EEG functional network obtained in this study using LORETA-ICA (independent component 13). The colors represent correlated and inversely correlated EEG power changes of brain regions (when neural activity in red colored regions increases, activity in blue colored regions decreases, and vice versa). The component covers activity within the delta, theta and alpha frequency bands in different parts of the brain. Frontally (Brodmann area [BA] 6 and 8 to 10), left-sided alpha power is inversely correlated with

right-sided delta and theta power. Occipitally (BA 17 to 19), there is a notable right-left asymmetric neural activation (i.e. negative correlation), inversely for alpha and theta power, whereas there is a diffuse activation and deactivation of delta power. Most evident is delta activation seen at a large area surrounding the left lateral sulcus including parts of the parietal (somatosensory cortex, BA 1 to 3; supramarginal gyrus, BA 40), temporal (Wernicke’s area, BA 22), and frontal (motor cortex, BA 4 and 6; Broca’s area, BA 44) lobe. Given the participating brain regions, we termed this network the prefrontal-sensorimotor (PF-SM) network.

Figure 4

ROC (receiver operating characteristic) curves for the prediction of remission by the prefrontal-sensorimotor (PF-SM) network loading and age as predictors (A), and all predictors (i.e. network loading, age, and baseline symptom severity; B). Red and blue lines represent outcome after rTMS treatment in women and men, respectively (dataset 2). Green lines represent outcome after sertraline treatment in women and men (dataset 3). The area under the curve (AUC) for each model is displayed in the figure.

Figure 5

The scatterplot (A) displays the change on the self-report questionnaires (standardized Δ BDI-II for the rTMS sample and Δ QIDS for the sertraline sample; positive values indicate improvement and negative values worsening of symptoms) and the individual loading on the prefrontal-sensorimotor (PF-SM) network. The colored lines represent the LOESS (locally estimated scatterplot smoothing; 75% points to fit) within the specified group. The vertical dotted lines, in subgroup corresponding color, represent the cut-off points which were determined by the maximum Youden's index. The stratification (B), allocated patients to different antidepressant treatments depending their network PF-SM loading (above or below

two cut-offs, see main text) and sex. The bar chart (C) represents the improvement of remission within subgroups after stratification (blue bars) relative to normalized non-stratified remission rates (red bars).

Supplementary Files

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