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A polygenic-informed approach to a predictive EEG signature empowers antidepressant treatment prediction: *A proof-of-concept study*

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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 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 predic-

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tion model with age and baseline severity data (area under the curve, AUC=0.623 for medicaton; 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 validation 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.

1. 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 et al., 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 (Fabbri et al., 2018; Garriock et al., 2010; Ising et al., 2009; Ji et al., 2013; Li et al., 2016, 2020a; Tansey et al., 2012; Uher et al., 2010). 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 (Fanelli et al., 2021, 2020; Foo et al., 2019; García-Gonzáleza et al., 2017; Li et al., 2020; Pain et al., 2020; Ward et al., 2018). 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 et al., 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 et al., 2017, 2016; Olbrich and Arns, 2013) as well as rTMS outcome (Arns et al., 2014; Erguzel et al., 2014; Hasanzadeh et al., 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 validated (Aoki et al., 2015; Gerrits et al., 2019) 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 psy-

chotherapy in male MDD patients in an independent dataset. Finally, we analysed the prediction accuracy of treatment response in male MDD patients based on the discovered EEG signature.

2. Materials and Methods

2.1. 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 to use a data-driven-data-reduction into fICA components that would be transdiagnostic and explain most of the variance, rather then 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 (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.

2.2. 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 et al., 2016, 2015).

2.3. 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).

2.4. Participants of the psychotherapy study, dataset 4

The fourth 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.

2.5. 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 (dataset 2, 3 and 4; 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, 3 and 4), 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 et al., 1983); 4) segmentation in 4-second epochs; and 5) 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.

2.6. 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 (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 identify 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).

2.6.1. 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 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, 3 and 4. Likewise, for each subject in each dataset, EEG component scores

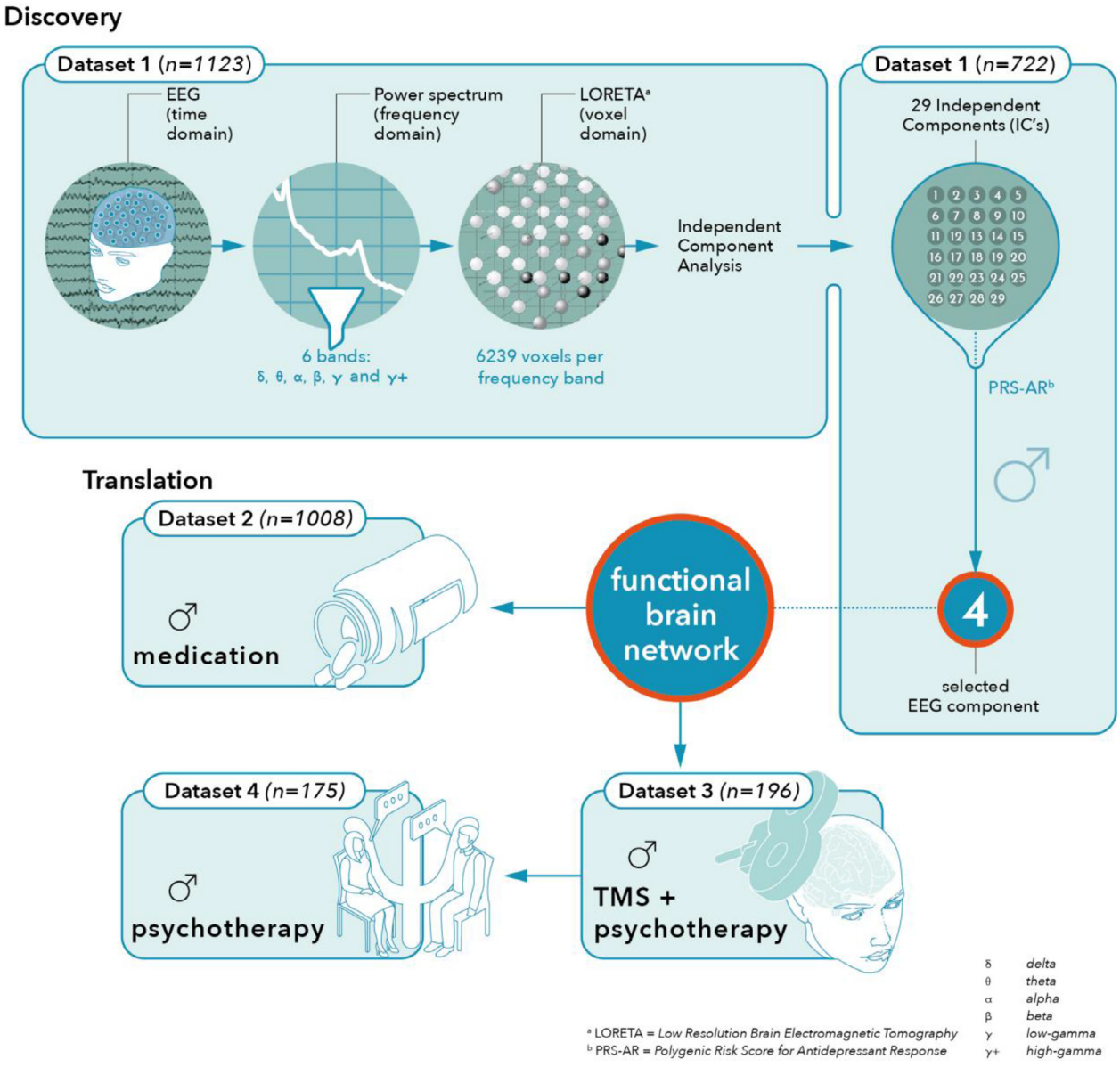

Fig. 1 Chart depicting the study set-up and analysis pipeline.
The LORETA-fICA method was used in the discovery analysis. Data for this method consisted of 6 a priori defined frequency bands and 6239 voxels (6 × 6239) per subject (dataset 1). This resulted in 29 independent cross-frequency spectral-spatial components. In male participants, only fICA EEG components 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.

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

2.7. Outcome measures

For component selection (discovery, Fig. 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, Fig. 1). Outcomes were based on the QIDS or BDI-II (dataset 2 and 3).

2.8. 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 separetaly, 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 (Arns et al., 2016, 2015; Dinteren et al., 2015; 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 Fig. 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 ($P_T=5.0 \times 10^{-6}$ to $P_T=1$) in order to choose the optimal P_T, which is unknown a priori (Choi et al., 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 non-responders. 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 as covariate 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 (Arns et al., 2016; Krepel et al., 2019; Saveanu et al., 2015). 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 cuf-off for rTMS with concurrent psychotherapy. Subsequently, the PPV and NPV were calculated in a crosstabulation including all male patients. A sensitivity analysis consisting of the subgroups CBT versus other psychotherapy was also performed.

3. Results

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

3.1. 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 diagnozed 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 Fig. 1: discovery).

3.1.1. 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). 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

Table 1 Baseline characteristics.

	Dataset 1:"discovery"	*Dataset 3:medication*	*Dataset 2:rTMS + PT*	*Dataset 3:psychotherapy*
Total 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

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.

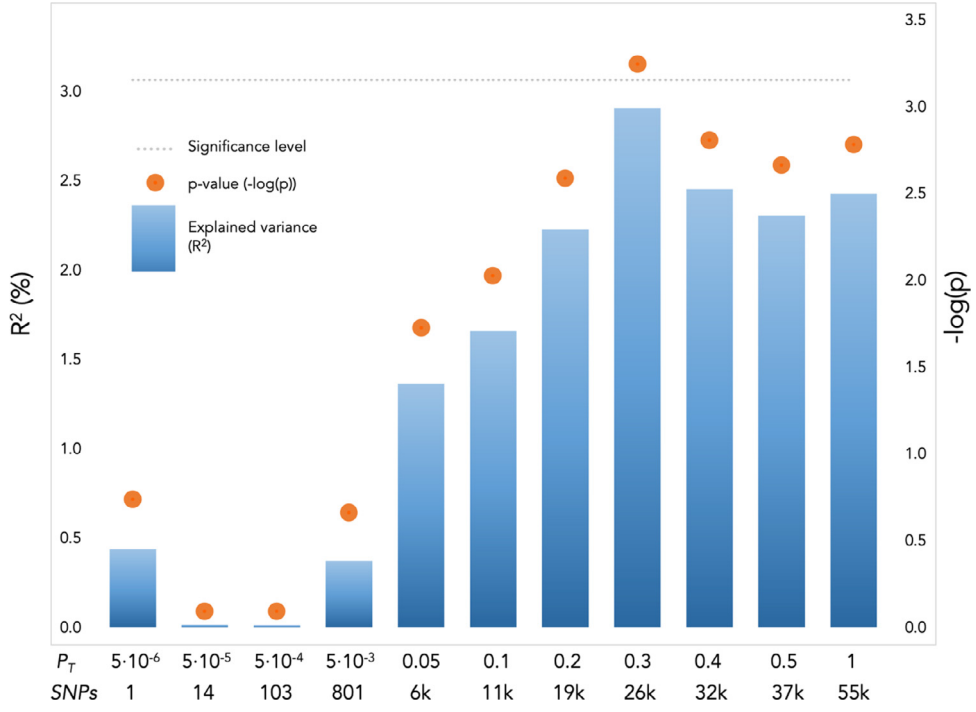

Fig. 2 Polygenic risk regression model of antidepressant response in men using different p-value thresholds.
The graphs show the explained variance (R^2 as %) of EEG component 4 in men by PRS-AR (polygenic risk score of antidepressant response [improvement]; blue bars), and the corresponding p-value (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.

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 Fig. 2).

Fig. 3 shows fICA EEG component 4 (this component explaines 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 left dorsolateral prefrontal cortex (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 individueal EEG component 4 scores only correlated with some non-EEG related baseline characteristics in women, not in men.

3.2. Translation and discovery analysis in an independent treatment reponse dataset (dataset 2 and 3)

The primary outcome for translational analysis (see Fig. 1: translation) was dimensional improvement of depres-

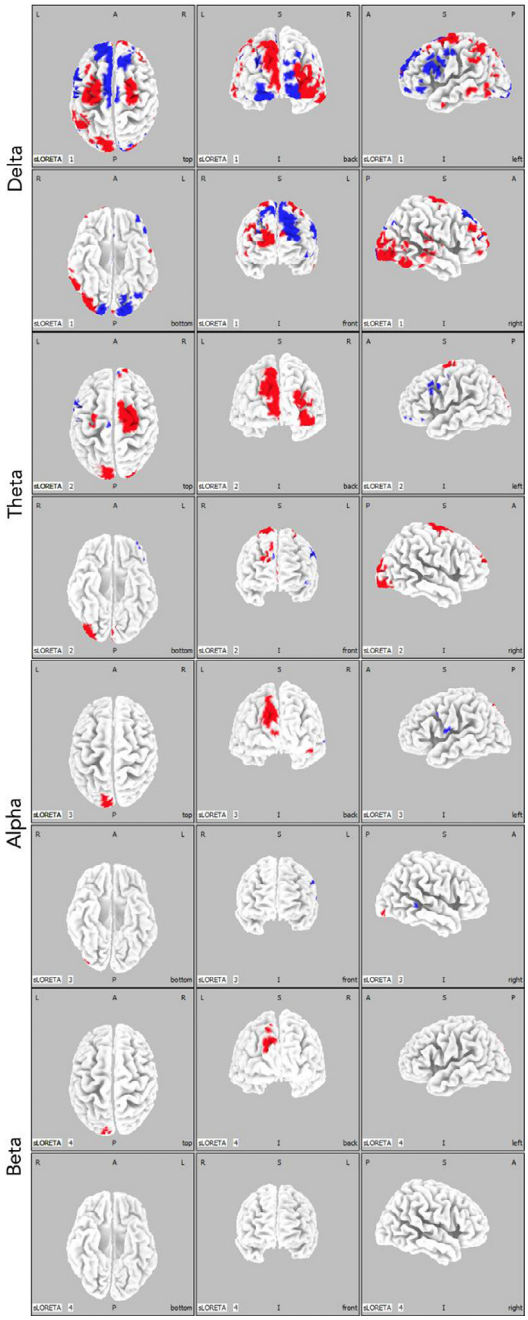

Fig. 3 Functional network of the component obtained with LORETA-ICA.
Map of the EEG functional network obtained in this study using LORETA-ICA (independent component 4). The colors represent correlated and inversely correlated EEG power changes of brain regions (when neural activity in red colored regions 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).

sive symptoms and secondary was categorical response (defined as $\geq$50% reduction of baseline score), based on the BDI-II at baseline and after rTMS. Data were normally distributed.

3.3. 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 $\times$ 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 Fig. 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).

3.4. 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 measures (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 vari-

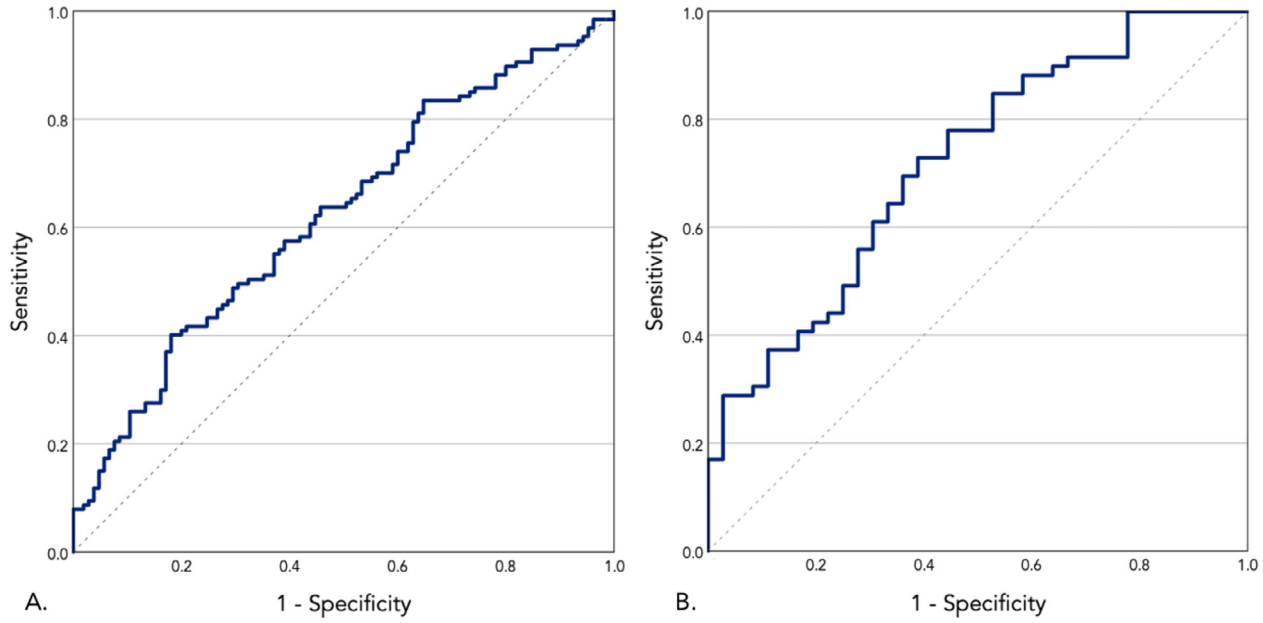

Fig. 4 ROC curve of the improved treatment prediction model for response.
ROC (receiver operating characteristic) curve for the prediction of medication response (A) and rTMS and concurrent psychotherapy response (B) by the EEG component, age and baseline symptom severity as predictors (improved model),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

able 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 signifincantly predict treatment response in men ($\Lambda=0.929$; $\chi^2=6.739$; $p=0.034$), but adding EEG component 4 improved the model ($\Lambda=0.859$; $\chi^2=13.914$; $p=0.003$) with a PPV of 76% and the ROC for this analysis (see Fig. 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 ($\Lambda=0.930$, $\chi^2=6.698$, $p=0.010$).

3.5. 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 of EEG as single predictor. 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).

3.6. 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%).

4. Discussion

Given psychological measures mapping poorly on neurobiology and cognizant of the scarce diagnostic and prognostic biomarkers in MDD (Krepel et al., 2019; Saveanu et al., 2015; Vinne et al., 2017), 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 (Fig. 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 et al., 2018). TMS applied to the PFC, however, results in transsynaptic activation of deeper areas such as the sgACC (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 outcome 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 reponse 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 reponse 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 treaments, 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 (Barth et al., 2016; Simon, 2002; Voigt et al., 2019), and antidepressant discontinuation and switching rates are high (Demyttenaere et al., 2001; Goethe et al., 2007; Mullins et al., 2005), 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.

Author contributors

All authors have approved the submitted version and agreed to be personally accountable for their own contributions. Data collection: JJL, BdW, JvH, PN and MA. Processing of data: HM, BL, KvE and MA. Statistical analysis: HM, AP and MA. Supervision: JJL and MA. Writing, original draft: HM. Writing, review & editing: all authors.

Declaration of Competing Interest

MA is unpaid chairman of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications related to EEG, neuromodulation and psychophysiology, but receives no royalties related to these patents. The authors, HM, AP, BL, BdW, JvH, PN, KvE, JJ and MA, declare no competing financial or non-financial interest.

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Data and materials availability

The data that support the findings of this study are available from the corresponding author, MA, via https://brainclinics.com/resources/ or on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.07.006.

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