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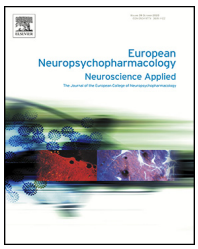

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EEG biomarker informed prescription of antidepressants in MDD: a feasibility trial

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Abstract
Using pre-treatment biomarkers to guide patients to the preferred antidepressant medication treatment could be a promising approach to enhance its current modest response and remission rates. This open-label prospective study assessed the feasibility of using such pre-treatment biomarkers, by using previously identified EEG features (paroxysmal activity; alpha peak frequency; frontal alpha asymmetry) to inform the clinician in selecting among three different antidepressants (ADs; escitalopram, sertraline, venlafaxine) as compared to Treatment As Usual (TAU). EEG data were obtained from 195 outpatients with major depressive disorder prior to eight weeks of AD treatment. Primary outcome measure was the percentage change between before and after treatment on the Beck Depression Inventory-II (BDI-II). We compared TAU and EEG-informed prescription through AN(C)OVAs. Recruitment started with patients receiving TAU

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to establish baseline effectiveness, after which we recruited patients receiving EEG-informed prescription. 108 patients received EEG-informed prescription and 87 patients received TAU. Clinicians and patients were satisfied with the protocol. Overall, 70 (65%) of the EEG-informed clinicians followed recommendations (compared to 52 (60%) following prescriptions in the TAU group), establishing feasibility. We here confirm that treatment allocation informed by EEG variables previously reported in correlational studies, was feasible.

1. Introduction

The treatment of major depressive disorder (MDD) is characterized by modest response and remission rates, while the disease affects increasing numbers of people worldwide, from 183 million in 2005, to 216 million in 2015 (Vos et al., 2016). Clinical efficacy ranges from 37% remission after a first antidepressant (AD) prescription to declining remission rates of respectively 31%, 14%, and 13%, after each consecutive AD trial, including augmentation strategies (Rush et al., 2006).

One way to improve response and remission rates in the early AD treatment steps for MDD is to better target the medications to particular patients. In that regard, identification of pre-treatment biomarkers which can inform choices between or among treatments offers a promising approach, although a need for replication and out of sample validation have been suggested (Widge et al., 2019).

To develop such biomarkers, the iSPOT-D research group collected pre-treatment EEG data (International Study to Predict Optimized Treatment; Saveanu et al., 2015; Williams et al., 2011). The initial phase of the study randomized 1008 patients with non-psychotic MDD to eight weeks of treatment with either escitalopram, sertraline or venlafaxine-XR. Overall response (62%) and remission (46%) rates did not distinguish among these three medication groups, indicating comparable clinical efficacy on the *group-level* based on randomized treatment allocation.

Furthermore, several EEG parameters were investigated as predictors for response and remission (using pre-registered hypotheses). Three promising biomarkers emerged that seemed to inform which patients are preferentially served by which AD medication, as both drug-specific as well as drug-class specific predictors, opening up the possibility for EEG-guided treatment (or stratification). The first was frontal alpha asymmetry (FAA): Right FAA was found to be related to response and remission (and left FAA to non-response and non-remission) to the SSRIs escitalopram and sertraline in females only. No such effect was observed for the SNRI venlafaxine (Arns et al., 2016). A post-hoc simulation showed that assigning patients to an SSRI or SNRI merely based on their FAA, resulted in a 7-14% higher remission rate (Arns et al., 2016). This study replicated findings of Bruder et al. (2001). The second biomarker was alpha peak frequency (APF): A low APF was associated with better response to sertraline and no effects for escitalopram and venlafaxine (Arns et al., 2017). The third biomarker was abnormal EEG activity: abnormalities like isolated epileptiform discharges (IEDs) were associated with non-response to escitalopram and venlafaxine, and no such effect for sertraline (Arns et al., 2017). In addition, EEG normalization after eight weeks on sertraline mediated AD response, suggesting sertraline specifically worked on the reported EEG abnormalities (van der Vinne et al., 2019a).

In summary, our prior work revealed drug-specific (sertraline), drug class-specific (selective serotonin reuptake inhibitor (SSRI) vs. serotonin norepinephrine reuptake inhibitor (SNRI)) and sex-specific EEG parameters that could aid in resolving the heterogeneity in clinical response to ADs, and that could be used to choosing among ADs, going from a stepped-care approach to a biomarker-informed approach.

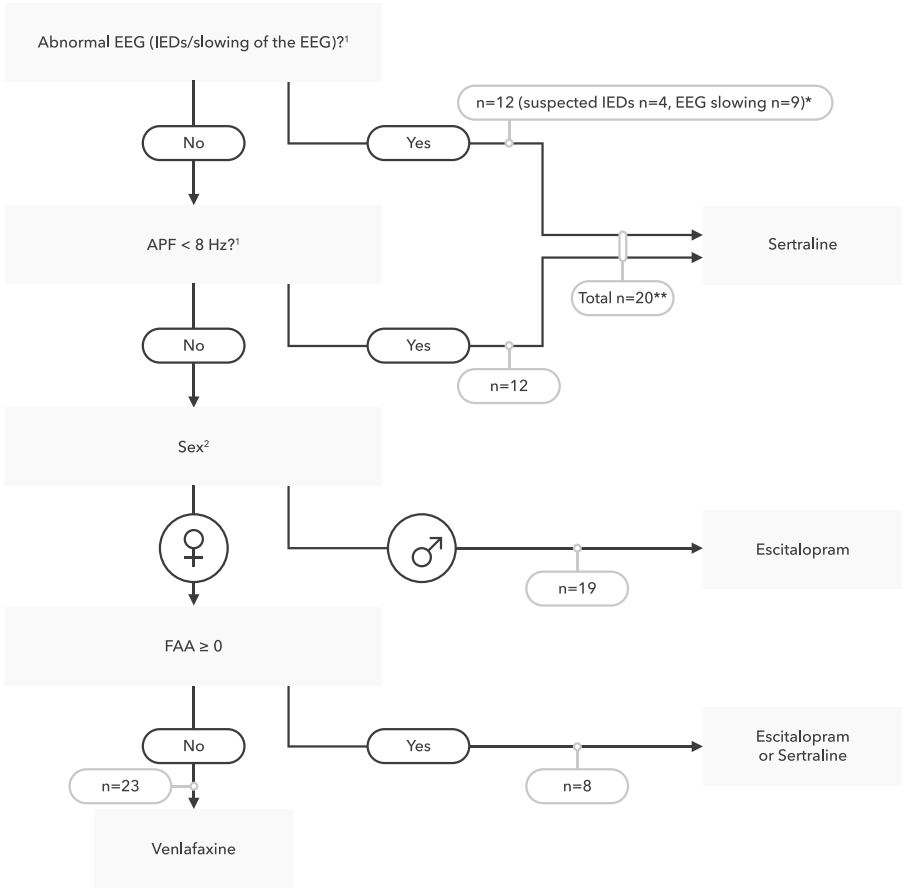
In order to determine whether medication could be prescribed based on these baseline EEG biomarkers, we conducted a prospective feasibility trial, in which we compared EEG-informed treatment recommendation with Treatment As Usual (TAU). We report our findings in developing and implementing this clinical decision-making tool and providing power calculations to inform future clinical trials. Our null hypothesis was that clinical response is not worse for EEG-informed treatment allocation, compared to TAU. If, alternatively, EEG-informed prescription was better, we expected group differences to be small, given the comparison of two active treatments.

2. Experimental procedures

2.1. Design

This was an open-label, naturalistic study, which was deliberately chosen to mimic real-world practice, with the aim of optimizing the translatability to real world settings. We investigated 195 outpatients with non-psychotic MDD, recruited between June 2015 and July 2019 in an outpatient clinic in Leeuwarden, the Netherlands. The primary diagnosis of nonpsychotic MDD was confirmed by a psychiatrist or specialized clinical psychologist, according to DSM-IV criteria, and a score $\geq$14 on the Dutch 21-item Beck Depression Inventory Second Edition (BDI-II-NL, Beck et al., 1996; Van der Does, 2002). Only data from patients who were prescribed with ADs were included. All MDD patients were allowed to enter the study when already on an AD (since Van der Vinne et al. (2019b) demonstrated that the predictive value of FAA was not influenced by medication status). Only patients wishing to change their AD were included in the effectiveness study, therefore treatment response was recorded for only those who started a(n) (new) AD *after* EEG assessment. Patients signed an informed consent and data were coded anonymously.

To establish baseline effectiveness, recruitment started with MDD patients who had not received EEG-informed prescription, and received TAU. Once the biomarker algorithm based on our prior work was finished, we began to recruit patients for the second arm – those who were to receive EEG-informed prescription (see paragraph 2.2). After eight weeks of AD treatment, all patients



[1]Arns, M., Gordon, E., & Boutros, N. N. (2017).

[2]Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D. M., Etkin, A., . . . Gordon, E. (2016).

Fig. 1 Decision tree used for EEG-informed treatment allocation and clinical decision making. In the first step, sertraline was advised when a patient displayed subclinical abnormal EEG activity (IEDs or slowing of the EEG), or an alpha peak frequency (APF) below 8 Hz. For the second step, males were advised to start escitalopram (male response rates in Arns et al. (2016) revealed the best effect of escitalopram, regardless of FAA). For females, escitalopram or sertraline were advised for a right-sided FAA, and venlafaxine was advised when a left-sided FAA was observed.
*1 patient had both EEG slowing and suspected IEDs.
**4 patients had both a slow APF and EEG slowing/suspected IEDs.

were tested again using the BDI-II. Both EEG assessments and week-8 measurements were completed at a priori defined dates. Patients who did not complete eight weeks of treatment within the defined period, were excluded from analyses. Both dropouts and different recruitment periods accounted for different subsample sizes. As part of our feasibility report, we discuss reasons for dropout extensively in paragraph 3.2 and supplement S1.

2.2. EEG-informed protocol vs. TAU

Patients had to meet a DSM-IV classification for non-psychotic depression, and a BDI-score≥14. For those receiving EEG-informed prescription (for a full decision tree also see Fig. 1), the EEG outcome was shared with the designated nurse practitioner or psychiatrist. Together with the patient, it was decided whether the advice was to be followed. The clinician's decision on whether to follow the advice was leading, and the EEG recommendation was not binding. Without informed consent, the advice was still offered, but data were not recorded for scientific purposes nor included in this report.

In case of TAU, AD choice resulted from the prescriptive decisions of a psychiatrist or nurse practitioner. In case of a first depressive episode, the prescription of an AD was based on national guidelines for prescribing first-choice ADs. In case of a recurrent depression, applicable national guidelines were followed. Where available, information on earlier (un-)successful drug treatments of either the patient or first-degree relatives was considered.

Treatment and progress were monitored. BDIs were filled out at fixed times: at intake, prior to each form of medical treatment, and eight weeks after each started medication. Registration of clinical patient data consisted of the following variables: previous treatments, current and possible previous diagnoses/classifications, EEG (advice) outcome, medication during EEG, following or ignoring the advice, which AD was prescribed, which psychological treatment was followed, and all BDI measurements.

2.3. Pre-treatment assessments

EEG recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Details of this procedure (Arns et al., 2016) and of its reliability have been published elsewhere (Paul et al., 2007; Williams et al., 2005). In summary, patients were seated in a sound and light attenuated room. EEG data were acquired from 26 channels: 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 (ANT Waveguard-cap; NuAmps; 10-20 electrode international system). EEG was assessed for two minutes with eyes open (EO, with the patient asked to fixate on a red dot on the screen) and two minutes with eyes closed (EC). The patient was instructed to remain relaxed for the duration of the recording. The operator did not intervene when drowsiness patterns were observed in the EEG. Data were referenced to averaged mastoids 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. Skin resistance was $<$10K Ohms for all electrodes. The sampling rate of all channels was 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

2.4. EEG processing

EEG processing was conducted similarly to Arns et al. (2016), and performed by Brain Resource. In summary, data were (1) filtered (0.3–100 Hz and notch); (2) EOG-corrected using a regression-based technique similar to that used by Gratton et al. (1983); (3) segmented in 4-s epochs (50% overlapping) and an automatic deartifacting method was applied. This EEG processing pipeline was also validated against an independent manual-processing pipeline. The screening for subclinical EEG abnormalities was performed by trained psychologists (NvdV and MA), according to methods described in Arns et al. (2017). Eyes closed awake EEG data were examined for the presence of any focal or generalized slowing (EEG slowing). Diffuse slowing was recorded if the background frequency was consistently below the alpha range (Niedermeyer, 2005). Focal slowing was recorded if rhythms slower than alpha (theta or delta, i.e. $<$8 Hz) were consistently detected in a particular location (Krauss et al., 2010). Epileptiform or paroxysmal activity were defined as any EEG pattern (with or without a sharp contour) that emerges and disappears paroxysmally from the ongoing background activity (Niedermeyer, 2005). Non-paroxysmal, focal or generalized, slow wave activity were continuously recorded (note that records were almost entirely fully awake records) with some waxing and waning (Sharbrough, 2005). Finally, the presence of any of the so-called controversial waveforms (e.g., wicket spikes) was also recorded. These waveforms are paroxysmal but are of uncertain significance (Boutros et al., 2014). When an EEG provided inconclusive patterns or events, a board-certified neurologist/clinical neurophysiologist was consulted (MvP). EEGs of patients with TAU were not analyzed.

Choosing biomarkers for the protocol was based on the robustness and suitability suggested by earlier findings. Other proposed biomarkers were not chosen because of various reasons. Rostral anterior cingulate cortex (rACC) theta related to symptom improvement (Pizzagalli et al., 2001; 2018) was not replicated (Arns et al., 2015). Furthermore, the EMBARC trial demonstrated that rACC theta was not specific in response prediction, since it was associated with both sertraline as well as placebo response (Pizzagalli et al., 2018). EEG vigilance measures from Olbrich et al. (2016) were not implemented because the full details were not available yet at the time of initiating this study.

To determine EEG-informed prescription to AD, we employed the algorithm displayed in Fig. 1. In summary, EEGs showing abnormal activity conform Arns and colleagues Arns et al. (2017) received sertraline. When EEGs were deemed normal, FAA was assessed through the formula $(F4-F3)/(F4+F3)$, utilizing corresponding electrodes conform the 10-20 system. Females with right-sided FAA received either escitalopram or sertraline. Those with left-sided FAA received venlafaxine. Males received escitalopram after both outcomes: Arns et al. (2016) showed the best response and remission rates for this AD in males, regardless of FAA lateralization.

2.5. Statistics

Clinical response was determined after eight weeks treatment with the improvement as assessed by the BDI-II as primary outcome measure. The %BDI change from baseline to week-8 was chosen for analyses due to its normal distribution (as opposed to the non-normally distributed absolute difference). Remission was defined as a BDI-II score $\leq$12 and response was defined as a $\geq$50% reduction after eight weeks. Differences in age, sex, depression severity at baseline, and whether psychotherapy supplemented medication, were tested using one-way ANOVA or non-parametric tests, depending on distributions or variable type (continuous or binomial). When group differences were significant, the respective variable was added to the main analysis as covariate or fixed factor, depending on its nature.

The main analysis consisted of a univariate ANOVA, for investigating group differences in %BDI-II change. Significant effects were complemented with Cohen's *d* effect size and Number Needed to Treat (NNT, http://www.clincalc.com), based on %BDI-II change. In addition, odds ratios (ORs) were calculated for group differences in remission and response rates. Given this feasibility trial was expected to have insufficient statistical power to distinguish the groups and we had clear a priori expectations of the direction of effects (Ruxton and Neuhäuser, 2010), one tailed statistics were used to prevent overlooking relevant findings that require further investigation in future trials. Statistical significance was therefore set at $p < .10$. Statistical power analyses to inform future trials were performed to derive minimum sample sizes for adequate study power (http://www.clincalc.com).

3. Results

A total of 122 MDD patients who completed both baseline and week-8 assessment and met inclusion criteria, were included in our analyses, 70 with EEG-informed prescription and 52 controls with TAU. Dropout reasons and attrition are reported in great detail in supplement S1. Table 1 shows demographic and clinical information for included patients. There were no differences between the two treatment groups regarding age (Mann-Whitney *U*), sex and concurrent psychotherapy (χ^2). Patients with TAU had significantly higher BDI scores at baseline than those with EEG-informed prescription (Mann-Whitney *U*, $p = .048$). Table 2 contains all feature outcomes that were used for executing the protocol.

3.1. Feasibility

For an extensive qualitative analysis of the study's feasibility, we refer to supplement S1. In general, both clinicians

Table 1 Demographic features of the two patient groups.

	TAU	EEG-informed	Total
n	52	70	122
Females *n* (%)	25 (48%)	44 (62%)	69 (57%)
Average age (years M(SD))	37.2 (14.54)	40.3 (14.85)	38.9 (14.74)
BDI-II baseline (M(SD))	35.4 (9.61)	31.7 (10.56)	33.3 (10.28)
Supplemented psychotherapy	42 (71%)	50 (71%)	82 (71%)

TAU = treatment as usual, BDI-II = Beck's Depression Inventory II.

Table 2 Feature prevalence in the EEG-informed group.

	Suspected IEDs and/or EEG slowing (*n*)	APF (Hz; M, SD)	Slow APF <8 Hz (*n*)	FAA (M, SD)	FAA left-sided /right-sided (*n*)	Total (*n*)***
Total	12*	9.58 (1.29)**	12	−0.0132 (0.057)	34/16	70
Female	8	9.50 (1.36)**	7	−0.0178 (0.057)	23/8	44
Males	4*	9.72 (1.17)	5	−0.0057 (0.057)	11/8	26

* 1 subject showing both.
** Excluding 1 patient with a low voltage EEG: no alpha activity was visible.
*** Total n is less than the enumeration of the features in the respective rows: 4 subjects have both a slow APF and suspected IED/EEG slowing (2 females, 2 males).

and patients were satisfied with the new protocol. The practical implementation in the regular logistics of this Dutch mental health outpatient clinic proved to be feasible. Out of 195 initially included patients, we were able to analyze 122 (70 EEG-informed, 52 TAU). Attrition was mostly due to patients not filling out questionnaires at week 8 (10%), and patients stopping taking the AD (6%), which was not specific to the EEG-informed group. Other specific attrition reasons for the EEG-*informed* group were choosing a different AD due to earlier experience with the advised AD (4%), wanting to remain with their current AD, which was not the advised AD (3%), and the clinician choosing a different AD (5%).

3.2. Treatment outcome

The EEG-informed prescription group demonstrated significantly better response (%BDI-II change) relative to the TAU group ($F(1,120) = 5.235$, $p = .024$), with a small to medium effect size of $d = 0.42$ and NNT of 8. A sensitivity analysis with the addition of covariate baseline BDI-II score to the model, yielded the same significant effect ($F(1,119) = 4.612$, $p = .034$) with the covariate itself being non-significant ($F(1,119) = 0.321$, $p = .572$). Treatment outcome can be found in Table 3. Interestingly, in the EEG-*informed* group the representation of the three ADs was quite comparable on the group level ($n = 22$–24 per AD) and clinical benefit per individual drug was also quite comparable (range: 35.1–38.5% BDI-II change, not significantly different between drug groups), similar to the iSPOT-D study. See Table 3.

Intention to treat analysis
With large dropout rates in both groups, we performed an intention to treat (ITT) analysis ($n = 195$). All dropout patients were assigned their baseline BDI-II value and thus assigned scores of 0% change on BDI, response and remission. Repeating the treatment outcome analyses yielded similar group difference for %BDI change ($F(1,193) = 3.726$, $p = .022$).

3.3. Future sample size calculation

Statistical power calculation showed that with an alpha set on 5%, a power of 85%, and an enrollment ratio of 1:1.2 (TAU:EEG-informed, based on current subsample sizes) a total of at least 213 participants would be required to have sufficient statistical power (97 patients with TAU and 116 patients with EEG-informed prescription). This was based on the primary outcome measure, percentage improvement on the BDI-II.

4. Discussion

We sought to prospectively test three previously identified EEG biomarkers using a feasibility trial. The implementation of the EEG-informed medication prescription algorithm proved feasible. The algorithm was sufficiently practical and satisfactory. The involved professionals were motivated to follow instructions and advice. It led to EEG-based prescription in 99 of 108 patients who received an EEG advice (89%), of which treatment outcome was known in 70 patients (65%). Major reasons for attrition were not specific to the EEG-informed algorithm, but related to patients not filling out questionnaires at week 8 (10%) or patients stopping taking the AD (6%). Most prominent attrition rates specific to the EEG-informed procedure comprised 12 subjects (11%) who either chose a different AD due to earlier experience with the advised AD, wanted to remain with their current AD which was not the advised AD, or for whom the clinician chose a different AD.

EEG-informed prescription resulted in significantly improved effectiveness with a small to medium effect size ($d = 0.42$), with response rates increasing from 27% to 39%,

Table 3 Treatment outcomes for the two patient groups.

	TAU	EEG-informed	Total
n	52	70	122
BDI-II baseline to week 8	35.4-27.1	31.7-20.2	33.3-23.1
% BDI-II change (below per medication and per sex (in italic))	23.9%*	36.8%*	31.3%
Escitalopram	*34.3% (n = 20)*	*35.1% (n = 24)*	
Sertraline	*23.5% (n = 8)*	*38.5% (n = 24)*	
Venlafaxine	*18.1% (n = 8)*	*36.7% (n = 22)*	
Duloxetine	*10.2% (n = 6)*	–	
Bupropion	*1.0% (n = 2)*	–	
Fluoxetine	*25.5% (n = 2)*	–	
Nortriptyline addition	*10.0% (n = 2)*	–	
Vortioxetine	*36.0% (n = 2)*	–	
Mirtazapine addition	*26.0% (n = 1)*	–	
Paroxetine	*-7.0% (n = 1)*	–	
Female/Male	*28.7%/19.4%*	*38.3%/34.3%*	
Normal EEG	-	*37.9%/36.1%*	
Abnormal EEG	-	*39.2%/29.3%*	
Remission	17%	29%	24%
Female/Male	16%/19%	32%/23%	
Response	27%	39%	34%
Female/Male	28%/26%	39%/38%	

TAU = treatment as usual, BDI-II = Beck's Depression Inventory II.
* $p < .05$

remission rates increasing from 17% to 29%, and an NNT of 8.

The TAU group presented with significantly higher baseline BDI scores. However, this is unlikely to affect the above conclusion, since baseline BDI did not interact with the percentage BDI change. This is in line with a large meta-analysis by Guo and colleagues showing a uniform effect of ADs, despite baseline severity differences (2020). Furthermore, if higher baseline severity would have any effect, more room for improvement would be expected with a regression to the mean in the TAU group (Mora et al., 2011). This would be expected to be seen in Food and Drug Administration phase II and III trials already (Khan et al., 2002). Since we found an opposite effect, the lack of covariate influence implies even less likely that the group difference at baseline affected our main outcome.

To acquire sufficient statistical power for determining meaningful group differences in future controlled trials, we have established that it is feasible to recruit patients in new trials. Power calculation indicated that future trials using clinical improvement on the BDI-II over an 8-week period of treatment as their primary endpoint, would require 218 patients. These numbers refer to patients with analyzable data, given the attrition rate of 35%. Attrition rates in future trials will presumably be lower, given the naturalistic character of our study, and the average of 30% in a large review of AD trials (Woolley et al., 2009). Assuming an attrition rate of 30% suggests a future trial sample of 311 patients.

This first evidence from a prospective replication study, provides the first steps to a future where EEG biomarkers can be used to inform clinical decision making, in this case treatment selection.

Recently, this particular application of EEG biomarkers was questioned, for publication bias, lack of proper replication studies, and out of sample validation (Widge et al., 2019). The present results provide the first prospective test of a priori defined EEG biomarkers, and thus provide strong evidence for the clinical use of these biomarkers, which should be confirmed in future controlled randomized controlled studies. In addition to the presence of EEG abnormality favoring response to sertraline (Arns et al., 2017), we previously have demonstrated that the degree of EEG normalization after eight weeks of treatment with sertraline, mediated clinical response (van der Vinne et al., 2019a). These results suggest that sertraline impacts mechanistically on this EEG abnormality, i.e., by possibly having mild anticonvulsant properties. From a neurochemical perspective, it has been reported that sertraline, relative to other SSRIs, has the most pronounced dopamine transporter (DAT) inhibitory activity (Sanchez et al., 2014). Kanekar and colleagues also suggested a differential working mechanism in sertraline compared to other ADs, considering the increased inhibition of DAT by sertraline (Kanekar et al., 2018). Another explanation can be found in the possible seizure prevention of sertraline through decrease in cerebral presynaptic Na^{+} and Ca^{2+} channel permeability (Aldana and Sitges, 2012; Sitges et al., 2016; Sitges et al., 2016). Since these properties were not investigated in escitalopram or venlafaxine, a proper comparison cannot be made. Future studies should investigate the exact neurobiological underpinnings further.

For the neurobiological underpinnings of FAA, the question is which role it has in the functional networks involved in depression, especially as a reflection of deeper nodes such as the subgenual anterior cingulate and other limbic structures. Given that FAA was associated to blood-oxygen-

level-dependent (BOLD) activity in the left amygdala and emotion regulation (Zotev et al., 2016), FAA might reflect fronto-amygdala network activity. Previously reported amygdala AD response patterns (Carceller et al., 2018, in mice; Sheline et al., 2001 in humans) as well as sex differences within the amygdala (Douillard-Guilloux et al., 2017), could help explain the sex-specific ability of FAA in predicting treatment outcome. The evidence however, remains indirect. The lack of multimodal studies that provide insight into causal relationships currently limits our ability to explain the relevant underlying neural circuitry behind the FAA-SSRI-response association.

An important limitation of this study, is the lack of random assignment to the groups, and possible non-specific and/or expectancy effects. Allocated patients were aware that the prescribed medication was based on their EEG, which could have favored the EEG-informed arm. On the other hand, the results derived from this naturalistic set-up are more likely to generalize to clinical practice. Future studies should employ a randomized design where patients are unaware of how their assignment to treatment was done (e.g. TAU vs. EEG-informed). And longer follow-up periods are needed since non-specific (placebo) effects are usually brief. Furthermore, although we found no covariate influence of the significantly higher depression severity at baseline in the TAU arm, baseline differences could still bias our results. Such a bias can be reasoned by the notion that clinical observations sometimes suggest that patients with a more severe depression are harder to treat, which should be taken into consideration. Another limitation is the fact that patients were allowed to be on medication when their EEG was measured. While it has been shown that medication status does not influence the FAA biomarker (van der Vinne et al., 2019b), this has not been investigated for EEGs containing abnormalities or a low APF. Results are nevertheless promising, given our preliminary effect size of 0.4, compared to placebo controlled effect sizes of ADs of 0.3 (Cipriani et al., 2018). Further investigation in prospective clinical trials of this EEG-informed medication prescription is warranted.

4. Conclusions

To the best of our knowledge, this was the first prospective EEG biomarker-based allocation feasibility study in MDD using a priori defined EEG biomarkers. Our proposed protocol proved to be feasible, with more symptom improvement in patients allocated to ADs based on specific EEG biomarkers (FAA, APF, and paroxysmal activity). This improvement approached a medium effect size, despite the comparison of different patient groups taking the *same* AD treatments. Hence, it is very promising to follow up with clinical trials, on the road to personalized treatment, that might be preceded by EEG-informed treatment allocation as an intermediate step.

Role of funding source

The study had no funding source.

Contributors

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

NvdV designed the study, wrote the protocol, performed assessments, managed literature searches, undertook the statistical analyses, and wrote the first draft of the manuscript. MV designed the study, was involved in statistical analyses and writing the first draft of the manuscript. AJR provided extra statistical analyses and was involved in improving the manuscript. ME performed assessments and was involved in writing parts of the first draft of the manuscript. MvP was involved in creating the protocol and in improving the manuscript. MA designed the study, wrote the protocol, and was involved in writing the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

AJR has received consulting fees from Compass Inc., Curbstone Consultant LLC, Emmes Corp., Holmusk, Johnson and Johnson (Janssen), Liva-Nova, Neurocrine Biosciences Inc., Otsuka-US, Sunovion; speaking fees from Liva-Nova, Johnson and Johnson (Janssen); and royalties from Guilford Press and the University of Texas Southwestern Medical Center, Dallas, TX (for the Inventory of Depressive Symptoms and its derivatives). He is also named co-inventor on two patents: U.S. Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS; and U.S. Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S.

MvP is a co-founder of Clinical Science Systems.

MA is unpaid research director of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and is a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation and psychophysiology, but does not own these nor receives any proceeds related to these patents; Research Institute Brainclinics received research funding from Brain Resource (Sydney, Australia), UrgoTech (Paris, France) and neuroCare Group (Munich, Germany), and equipment support from Brainsway, Deymed, neuroConn and Magventure.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2020.12.005.

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