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EEG Abnormalities Are Associated With Poorer Depressive Symptom Outcomes With Escitalopram and Venlafaxine-XR, but Not Sertraline: Results From the Multicenter Randomized iSPOT-D Study

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Abstract

Rationale. Limited research is available on electrophysiological abnormalities such as epileptiform EEG or EEG slowing in depression and its association with antidepressant treatment response. *Objectives*. We investigated the association between EEG abnormalities and antidepressant treatment response in the international Study to Predict Optimized Treatment in Depression (iSPOT-D). *Methods*. Of 1008 participants with major depressive disorder randomized to escitalopram, sertraline, or venlafaxine-XR, 622 completed 8 weeks of treatment per protocol. The study also recruited 336 healthy controls. Treatment response was established after 8 weeks using the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). The resting-state EEG was assessed at baseline with eyes closed. EEG abnormalities including epileptiform activity, EEG slowing, and alpha peak frequency (APF) were scored for all subjects, blind to treatment outcome. *Results*. Patients and controls did not differ in the occurrence of EEG abnormalities. Furthermore, in the per protocol sample the occurrence of epileptiform EEG and EEG slowing (as a combined marker) were associated with a reduced likelihood of responding to escitalopram (P = .019; odds ratio [OR] = 3.56) and venlafaxine-XR (P = .043; OR = 2.76), but not sertraline (OR = 0.73). The response rates for this "any EEG abnormality" groups versus the "no-abnormality" group were 33% and 64% for escitalopram and 41% and 66% for venlafaxine-XR, respectively. A slow APF was associated with treatment response only in the sertraline group (P = .21; d = .027). *Conclusions*. EEG abnormalities are associated with nonresponse to escitalopram and venlafaxine-XR, but not sertraline, whereas a slow APF is associated to response for sertraline only.

Keywords

EEG, paroxysmal, epileptiform, alpha frequency, antidepressant

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Introduction

Since Hans Berger's[1] first description of the electroencephalogram (EEG), mainly visual inspection of the EEG (standard-EEG) was reported until the first applications of quantitative EEG or normative EEG were described.[2] The visual inspection of the EEG is the only currently available technique capable of reliably detecting paroxysmal isolated (ie, in the absence of clinical seizures) epileptiform EEG discharges (IEDs). This is more so when the discharges are relatively infrequent as is the case in psychiatric (nonepileptic) populations.[3] As early as in 1939, Schwab demonstrated that during generalized epileptiform activity patients had slower reaction times, while others did not respond at all (from Kasteleijn-Nolst Trenité and Vermeiren[4(p32)]), suggesting that IEDs in "non-epileptic patients" can have behavioral consequences. In addition, standard EEG is also capable of detecting gross slowing of EEG rhythms whether focally or diffusely indicating significant pathology. Generalized slowing of the EEG has been correlated with increased severity of psychiatric syndromes[5,6] and a slow background rhythm (slow alpha peak frequency [APF]) has been found to be a predictor for nonresponse to several treatments such as stimulant medication in attention deficit/hyperactivity disorder (ADHD),[7] repetitive transcranial magnetic stimulation (rTMS) in depression,[8,9] and the

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antidepressants pirlindol and amitriptyline[10]; for review, see Arns.[9] It is possible then, that in the presence of such EEG abnormalities, standard antidepressant treatments may not be the best pharmacotherapy approach for these individual patients.

Several other EEG metrics have been well investigated in their association with treatment outcome such as theta and alpha power (reviewed in Arns and Olbrich[11] and Olbrich and Arns[12]). However, these metrics more relate to differences in brain function within the normal range, whereas the EEG metrics focused on in this article focus more on "brain abnormality." The results of baseline alpha and theta measures in predicting treatment outcome to antidepressants on the same dataset as was used in this article have been published elsewhere.[13,14]

Previous reports have demonstrated that subgroups of patients with affective disorders do present with abnormally slow or IEDs either focal or generalized.[15-17] Conversely, depression is the most commonly reported psychiatric comorbidity in epilepsy.[18] The incidences of IEDs in affective disorders have not been investigated in much detail, but previous analyses suggest an incidence of 3% to 5% in depression[16] to 20% to 40% in affective disorders, mostly mania.[15] The 3% to 5% in depression is comparable to the 1% to 6% prevalence of paroxysmal EEG in normal populations.[7,15,19-21] The exact implications of IEDs in subjects *without* a history of clinical signs of seizures are under-investigated. Lennox-Buchthal et al[19] reported 3 times higher plane crash rates in fighter pilots with IEDs indicating that even though these individuals are not "epileptic," there could be pathological effects secondary to these EEG patterns. More specifically, several studies have demonstrated that the presence of IEDs has detrimental effects on neurocognitive function[4,22-24] and when treated with anticonvulsant medication neurocognitive improvements are observed.[22-24] Furthermore, an association between IEDs and panic attacks has been demonstrated (reviewed in Boutros et al[3]) and patients with panic disorder and IEDs have been found to clinically respond to anticonvulsant medication.[25]

In neurology, it is standard clinical practice not to treat these subjects with anticonvulsant medications, although in psychiatry often anticonvulsant medications to augment the effects of antidepressant medication are employed in treatment resistant depression, like in other psychiatric disorders such as panic disorders,[26] ADHD,[27-29] and autism.[30] Hence, these findings suggest the existence of a subgroup with IEDs, who might better respond to anticonvulsant medication.

Traditionally, slowing of EEG rhythms (whether focal or diffuse) are thought to reflect fundamentally different pathological processes (mostly hypofunctioning of the affected region) compared to the presence of IEDs (mostly reflecting hyperexcitability). However, slowing of EEG rhythms is frequently observed in patients without structural abnormalities.[31,32] In fact, it has been a consistent observation that regional EEG slowing is commonly present in temporal lobe epilepsy.[33] In a relatively recent article, Tao et al[34] reaffirmed that focal intermittent regional delta slowing could be a marker for an epileptic network. It is thus reasonable to predict that these EEG abnormalities would predict nonresponse to conventional treatments (eg, antidepressants), but could possibly predict differential response to different treatment modalities with the presence of IEDs predicting a favorable response to anticonvulsant medications.

In this study, we used data from the international multicenter Study to Predict Optimized Treatment in Depression (iSPOT-D: see William et al[35] and Saveanu et al[36] for details), which has a sufficiently large enough sample (1008 patients with major depressive disorder [MDD] and 336 controls) to obtain a sample of patients with IEDs or slow background rhythm and investigate the association with antidepressant treatment outcome. Detection of slow-wave abnormalities usually requires only a short recording and subjects being awake, while identification of IEDs depends to a significant degree on the duration of recording and recordings during drowsiness and light sleep. This study was not originally designed to investigate IEDs and only recorded 2 minutes of eyes-open and 2 minutes of eyes-closed EEG. These factors maximize the chances for a false negative recording for IEDs. Despite these limitations, we sought to capitalize on this large sample size of well-characterized patients with MDD to investigate if the presence of EEG abnormalities (slowing or IEDs) is associated with a poor treatment outcome to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). In addition, the individual APF for every patient was used as an additional measure allowing an analysis on the full sample.

This study was a secondary analysis of EEG data from the iSPOT-D study, and a proposal for analysis and a priori specified hypotheses were submitted and approved by the iSPOT-D publication committee before any analyses were performed. Our hypothesis was that nonresponders to the 3 antidepressant medications used in this study have a higher occurrence of IEDs and EEG slowing as well as a slower APF.

Method

Design

This study was an international multicenter, randomized, prospective open-label trial (phase IV clinical trial) in which MDD participants were randomized to escitalopram, sertraline, or venlafaxine-XR in a 1:1:1 ratio. The study protocol details have been published by Williams et al.[35] This design was deliberately chosen to mimic real-world practice—hence no placebo control was included—with the aim of improving the translatability of the findings and ecological validity.

Participants and Treatment

This study included 1008 patients with MDD and 336 healthy controls. A complete description of the study assessments, inclusion/exclusion criteria, diagnostic procedures and treatment is available in Williams et al.[35] In summary, the primary diagnosis of nonpsychotic MDD was confirmed at the baseline visit (before randomization) using the Mini-International

Neuropsychiatric Interview (MINI-Plus),[37] according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*) criteria, and a score ≥16 on the clinician-rated 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). All MDD participants were either antidepressant medication-naive or, if previously prescribed an antidepressant medication, had undergone a washout period of at least 5 half-lives before the baseline visit clinical and EEG assessments. After the baseline visit, MDD participants were randomized to 1 of the 3 antidepressant medications. After 8 weeks of treatment, participants were tested again using the $HRSD_{17}$. Average daily dosages for the 3 study medications and recommended dosages were as follows: escitalopram, 12.0 + 6.4 mg (recommended 5-20 mg); sertraline, 61.3 + 32.4 mg (recommended 50-200 mg); and venlafaxine-XR, 83.4 + 38.1 mg (recommended 75-225 mg.).[36]

This study was approved by the institutional review boards at all the participating sites. This trial was registered with ClinicalTrials.gov. Registration Number NCT00693849; URL http://clinicaltrials.gov/ct2/show/NCT00693849.

Pretreatment Assessments

EEG recordings were performed using a standardized methodology and platform (Brain Resource Ltd, Australia). Details of this procedure have been published elsewhere[7,35] and details of the reliability and across-site consistency of this EEG procedure have been published.[38,39] In summary, participants were seated in a sound and light attenuated room that was controlled at an ambient temperature of 22°C. 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 (Quikcap; NuAmps; 10-20 electrode international system). EEG data were collected for 2 minutes with eyes open (EO) and 2 minutes with eyes closed (EC). 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 3mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was <5 kohm for all electrodes. A continuous acquisition system was employed and EEG data were electro-oculogram (EOG)-corrected offline. 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.

Analysis

EEG Analysis. EEG data analysis and validation has been described in more detail elsewhere.[13] In brief, (1) a high-pass filter of 0.3 Hz, a low-pass filter of 100 Hz, and notch filters of 50 or 60 Hz (depending on the country in which the data were recorded) were applied; (2) data were EOG corrected using a regression-based technique similar to the method described by Gratton et al.[40] No other deartifacting was applied to the data other than EOG correction and filtering. Data were visually inspected in Brain Vision Analyser (Brainproducts, Germany) using a linked ears and queens-square montage. Visual inspection and classification was performed by a board-certified electroencephalographer, neurologist, and psychiatrist (N.N.B.) who was blinded to subject's group (patient vs control), clinical data, or treatment arm. Eyes closed awake EEG data were examined for the predominant background activity (including alpha peak frequency [APF]), and the presence of any focal or generalized slowing (EEG slowing). Diffuse slowing was recorded if the background frequency was consistently below the alpha range.[41] Focal slowing was recorded if rhythms slower than alpha (theta or delta, ie, <8 Hz) were consistently detected in a particular location.[42] 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.[41] Nonparoxysmal, focal or generalized, slow wave activity were more or less continuously present (note that records were almost entirely fully awake records) with some waxing and waning.[43] Finally, the presence of any of the so-called controversial waveforms (eg, Wicket spikes) was also recorded. These waveforms are paroxysmal but are of uncertain significance.[44] Classification of all abnormalities was in accordance to the guidelines published by the International Federation of Clinical Neurophysiology.[45]

Statistics

In this study, the primary outcome measure was treatment response, defined as a >50% decrease in $HRSD_{17}$ score from baseline to week 8. For $HRSD_{17}$ remission (defined as $HRSD_{17} \leq 7$), several baseline measures differed significantly that required statistical control (age, $HRSD_{17}$ severity and anxiety severity). Given the use of nonparametric tests (presence or absence of IEDs or EEG slowing), we hence decided to focus on $HRSD_{17}$ response. Differences in age, gender, and baseline depression severity were tested using 1-way analysis of variance or nonparametric tests (gender). For APF, a univariate analysis with dependent variable APF, fixed factors response and treatment arm and age as covariate were used and for the presence of IEDs or EEG slowing, chi-square tests were employed. Significance level was set at $P \leq .05$ and effect sizes of main effects are reported as Cohen's d or odds ratios with 95% confidence intervals (CIs). In this analysis, 3 main hypotheses were tested: Do nonresponders have a higher occurrence of (1) IED and (2) EEG slowing, and (3) do nonresponders have a slower APF.

Results

Of the 1008 MDD participants and 336 healthy controls enrolled, the final sample for this analysis consisted of 954 patients with MDD and 309 controls (for the MDD group 54 EEGs and for the control group 27 EEGs were unavailable or of insufficient quality for visual inspection). For the treatment

Table 1. Demographic Features of Patients With MDD and Controls With Complete Data and Treatment Outcomes for Patients Who Completed Treatment.[a]

Features	Controls	MDD	Escitalopram	Sertraline	Venlafaxine-XR
Number	309	954	204	225	193
Females	175	542	112	132	112
Average age (years)	36.78	37.85	38.59	38.50	38.42
$HRSD_{17}$ baseline	1.20	21.93	21.79	22.00	21.51
$HRSD_{17}$ week 8	1.11	9.64	9.15	9.39	9.71
$HRSD_{17}$ anxiety baseline	0.60	6.16	6.18	6.25	6.15
% Female	57	57	55	59	58
% Remission ($HRSD_{17}$)		46	50	47	44
% Response ($HRSD_{17}$)		63	62	67	64

Abbreviations: $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; XR, extended release.
[a]The demographics for the MDD versus controls comparison can be found left of the vertical line, whereas the demographics for the treatment prediction analyses are summarized to the right of the line (the per protocol sample).

prediction analysis (per protocol grouping) data from 622 MDD patients who completed the full 8 weeks of treatment were analyzed (main reasons for dropout were patients not starting the treatment, having less than 6 weeks of medication or having no week 8 assessment). In the completer sample, 46% reached remission and 63% reached response (see Table 1). No baseline demographic, social factors, or clinical features were related to treatment outcome, except anxiety, where greater anxiety levels were associated lower remission rates (see Saveanu et al[36] for a more detailed report of the sample and outcomes).

Participants With MDD Versus Controls

There were no differences between MDD and controls on age ($P = .198$; $F_{(1, 1262)} = 1.661$) and gender ($P = .956$; $\chi^2_{(1, 1263)} = 0.003$). Furthermore, there were no differences between MDD and controls in the occurrence of IEDs, EEG slowing or in APF (see Table 2).

Response Versus Nonresponse

Responders were younger (37.4 years, SD = 12.2) than nonresponders (40.4 years, SD = 13.0; $P = .004$; $F_{(1, 621)} = 8.175$), but did not differ in gender ($P = .605$; $\chi^2 = 0.268$). The occurrence of IED and EEG slowing were equal for the 3 treatment arms (all $\chi^2 > 0.5$), also see Table 2, panel B.

Alpha Peak Frequency. A main effect for age ($P = .008$; $F_{(1, 621)} = 7.139$), treatment arm ($P = .015$; $F_{(2, 621)} = 4.262$) and a response × treatment arm interaction ($P = .021$; $F_{(2, 621)} = 3.909$) were found. Repeating this analysis for the 3 treatment arms separately only yielded a main effect of response for sertraline ($P = .021$; $F_{(1, 224)} = 5.418$; $d = .27$) where responders had a slower APF (9.45 Hz; SD = 0.904) as compared with nonresponders (9.72 Hz; SD = 1.086). For escitalopram and venlafaxine-XR, the trends were opposite (as evidenced by the significant response × treatment arm interaction) but not significant (see Figure 1A).

Partial correlations covarying for age, yielded a trend for a correlation between APF and the percentage improvement on the $HRSD_{17}$ for sertraline ($P = .072$; $r_{(222)} = 0.120$) but not for venlafaxine-XR ($P = .107$; $r_{(190)} = -0.117$) and escitalopram ($P = .352$; $r_{(201)} = -0.066$), but no correlations or trends with baseline $HRSD_{17}$ were found (all Ps >.249).

IEDs and EEG Slowing. For the MDD group, 20 patients had IED and the occurrence was 4.5% in the nonresponse group and 2.5% in the response group, but this was not significant ($P = .175$). However, as can be seen in Figure 1B, there appeared to be an opposite association between treatment response and the occurrence of IEDs for sertraline as compared with escitalopram and venlafaxine-XR, comparable to the APF results above. Repeating this analysis for escitalopram and venlafaxine-XR yielded a 5.4% occurrence of IED in the nonresponder group compared with a 1.2% occurrence in the responder group, which was significantly different ($P = .014$; $\chi^2 = 6.080$), and an opposite nonsignificant ($P = .487$) effect for sertraline where the occurrence of IEDs was 4.6% in the responder group and 2.7% in the nonresponder group, also see Table 2, panel B for further details on frequencies.

For the EEG slowing group a similar pattern of results emerged. For escitalopram and venlafaxine-XR there was an occurrence of 3.6% in the responder and 8.8% in the nonresponder group ($P = .029$; $\chi^2 = 4.739$), and for sertraline there was a 7.9% occurrence in the responder group and a 6.8% occurrence in the nonresponder group ($P = .751$).

Repeating the analysis with a variable combining "any EEG abnormality" (including IEDs and EEG slowing) yielded a significantly lower occurrence of "any EEG abnormality" in responders to escitalopram (4.0% vs 12.8%; $P = .019$; OR = 3.56; CI = 1.147-9.101) and venlafaxine (5.7% vs 14.3%; $P = .043$; OR = 2.76; CI = 1.000-6.300) and no such effect for sertraline (12.6% vs 9.6%; $P = .491$; OR = 0.73; CI = 0.331-1.708), also see Figure 1B. Conversely, the response rates for the "any EEG abnormality" groups versus the "no-abnormality" group were 33% and 64% for escitalopram and 41% and 66% for venlafaxine-XR, respectively.

Table 2. The Occurrence of IED or EEG Slowing and Mean Alpha Peak Frequency (APF) Between MDD and Control Groups (A) and for the 3 Treatment Groups (B) for the Whole Group and Responders Separately.

	A				
	MDD (n = 954)		Control (n = 309)		
	n	%	n	%	*P*
IED	34	3.6	16	5.2	.206
EEG slowing	64	6.8	27	8.7	.231
APF, mean (SD)	9.56 (1.0) Hz		9.64 (0.85) Hz		.187

	B					
	Escitalopram (n = 204)		Sertraline (n = 225)		Venlafaxine-XR (n = 193)	
	n	%	n	%	n	%
IED	6	2.9	9	4.0	5	2.6
Responders	1	0.8	7	4.6	2	1.6
EEG slowing	10	4.9	17	7.6	12	6.2
Responders	4	3.2	12	7.9	5	4.1
APF, mean (SD)	9.41 (0.9) Hz		9.54 (0.9) Hz		9.69 (1.0) Hz	

Abbreviations: IED, isolated epileptiform EEG discharge; MDD, major depressive disorder; XR, extended release.

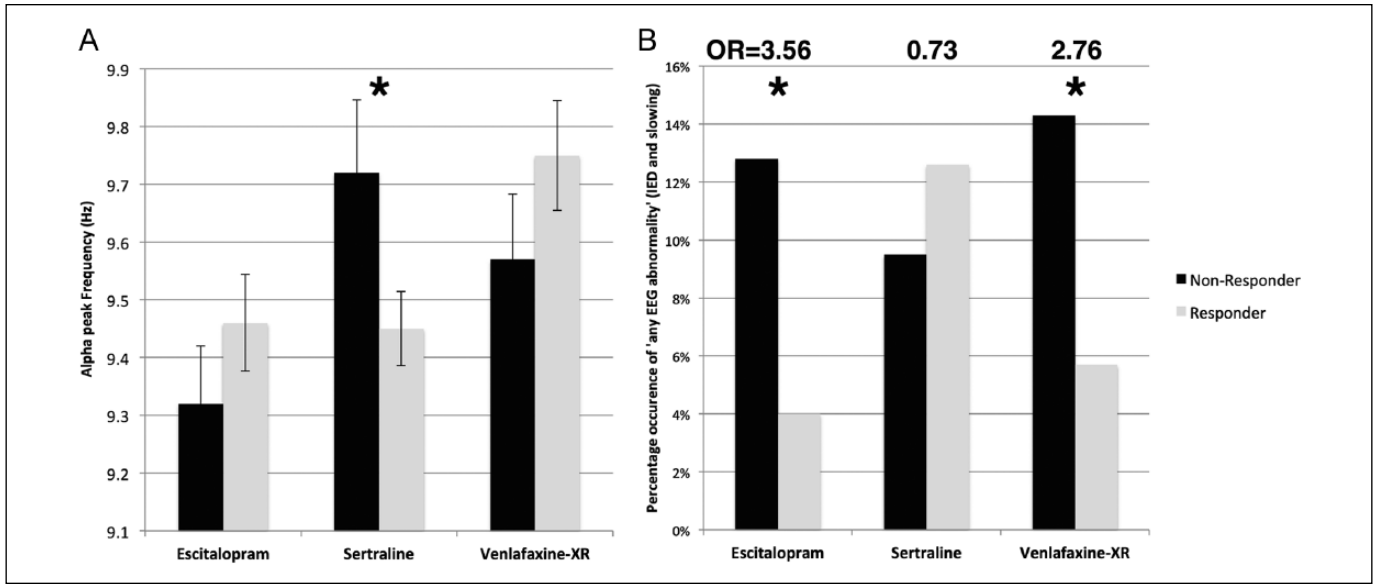

Figure 1. Difference in responders (light gray) versus nonresponders (black) in alpha peak frequency (APF) and EEG abnormalities. (A) Specifically sertraline responders exhibit a slower APF as compared with nonresponders and an opposite trend for escitalopram and venlafaxine. (B) Occurrence of "any EEG abnormality" (isolated epileptiform discharge [IED] and EEG slowing combined) for responders compared with nonresponders for the 3 study medications. Note the higher proportion of any EEG abnormality among nonresponders for escitalopram and venlafaxine, and no such effect for sertraline. OR = odds ratio; *$P < .05$; error bars represent standard error of the mean.

Post Hoc Analysis

Repeating the analysis for APF and sertraline after having excluded all subjects with an IEDs and EEG slowing, still yielded a trend for sertraline ($P = .064$; $F_{(1, 198)} = 3.463$; $d = .23$) with nonresponders having a faster APF (9.72 Hz) as compared with responders (9.5 Hz). This suggests the effect of APF cannot completely be explained by the presence of IED or EEG slowing.

In an earlier study on this sample looking at clinical variables associated with treatment response, only anxiety levels were found to be associated with treatment outcome in this sample,[36] hence we also conducted post hoc analyses checking if the current results could be explained by differences in baseline anxiety levels. The IED and EEG slowing groups did not differ in anxiety levels (all *P*s >.47), and adding baseline anxiety as a covariate to the APF analysis did not change the

results, therefore the observed associations in treatment outcome could not be explained by baseline differences in anxiety.

Discussion

In this study, no differences were found between patients with MDD and controls in the occurrence of EEG slowing, IEDs and APF This is in line with previous studies that reported similar rates of epileptiform EEG in MDD patients (3.6% to 5.3% in this study and 3% to 5% in the study by Arns[16]). Furthermore, as hypothesized, it was found that both the occurrence of epileptiform EEG and EEG slowing ("abnormal" EEG) was associated with a lower likelihood of responding to escitalopram and venlafaxine with ORs of 3.56 and 2.76, respectively. However, for sertraline this was not found (OR = 0.73). The fact that the same effects are found for both IED as well as EEG slowing provides concurrent evidence of brain-abnormality to be related to nonresponse to escitalopram and venlafaxine.

For APF we could not confirm our hypothesized association of a slow APF in nonresponders. However, the opposite finding was obtained for sertraline, where responders exhibited a slow APF, and this could not be explained by the presence of IED or EEG slowing. Therefore, these data suggest that even though sertraline is considered an SSRI, similar to escitalopram, its mechanism of action might be different in a clinically meaningful way. However, given this result was opposite to the hypothesized direction, this finding requires further replication.

Both the presence of IEDs, EEG slowing as well as a slow APF are well-accepted EEG abnormalities, these results tend to be suggestive of a response profile for sertraline characterized by a higher degree of EEG abnormality (ie, no association with nonresponse for IED or EEG slowing and a slow APF associated with response to sertraline).

What could explain this difference in response profile for sertraline as compared with the other SSRI escitalopram? A recent comparative review including escitalopram and sertraline[46] noted that differences between these drugs were (1) escitalopram has a slightly higher efficacy compared to sertraline, possibly the result of escitalopram's actions at allosteric sites of the serotonin transporter (SERT); (2) both drugs have a high affinity for SERT, but escitalopram has a higher selectivity (>1000-fold) as compared with sertraline (>60-fold); and (3) sertraline has the most pronounced dopamine active transporter (DAT) inhibitory activity and is associated with increased extracellular dopamine in nucleus accumbens, and striatum.[46] Furthermore, sertraline binds more to the dopamine D2 receptor [47]. Therefore, relative to sertraline, escitalopram could also be viewed as an Allosteric Serotonin Reuptake Inhibitor (ASRI) instead of an SSRI, and sertraline relative to escitalopram has a higher dopamine affinity via its DAT inhibitory activity and higher affinity to the D2 receptor. Further research is required to investigate if these differences can explain the low response rate of escitalopram in patients with IED and EEG slowing and the lack of such an association for sertraline (and higher response rate with a slow APF for sertraline).

Based on earlier work, we expected EEG abnormalities (IED, EEG slowing, and slow APF) to be associated with nonresponse to all three antidepressants. Furthermore, as suggested by Boutros et al[3] such a finding could have sparked more research on demonstrating *differential* effects of anticonvulsant medications in the IED subgroup. However, our results suggest that in patients with EEG abnormalities, escitalopram and venlafaxine-XR are not indicated, but given the lack of such an effect for sertraline, could implicate sertraline as a first choice, especially since this medication is already licensed as an antidepressant and could thus possibly substitute an off-label prescription (ie, anticonvulsant medication in depression). This finding could have direct relevance for treatment with rTMS where IED is a contraindication for treatment[47] and a slow APF has been found associated with nonresponse[8,9]; therefore such patients might preferably be tried on sertraline. Further research should compare the efficacy of sertraline compared with antiepileptic drugs in these subgroups to validate this notion further.

The exclusion criteria used in this study may have actively excluded mood disorder patients likely to have increased IED, such as excluding bipolar disorders[15] or patients with the characteristics of what has been termed subictal mood disorders or interictal dysphoric disorder,[48,49] possibly explaining the lack of a difference between MDD and controls. While this study by virtue of its large sample size and use of 3 different medications yielded interesting insights into the association between EEG abnormalities and treatment response, further limitations of this study include the limited amount of available EEG (2 minutes eyes closed), absence of data obtained during light sleep or drowsiness maximizing the potential for false negative findings for IED, the low numbers of IED subjects per subgroup and the fact that analyses were only performed on response and not remission. Future studies should adhere to the standards of clinical EEG recording[50] requirements of a minimum of 20 minutes including photic stimulation and at least 3 minutes of hyperventillation. The recordings should contain brief periods of stage 1 or stage 2 sleep.[51] Finally, all EEGs were evaluated by a single rater (N.N.B.); however, interestingly the percentages obtained in this study were almost identical to a previous study using data collected in an identical manner and comparable clinical (nonoverlapping) sample, rated by a different rater (3.6% to 5.3% this study compared with 3% to 5% in the study by Arns[16]), suggesting the use of a single rater most likely did not have a major influence.

A total of 10.3% of the patient sample exhibited demonstrable EEG abnormalities (IED or EEG slowing). While this rate did not differ from healthy controls, it takes on clinical significance as patients are symptomatic and the observed deviations may be contributing to their symptomatology.[44] Hence, it seems reasonable to suggest that the raw EEG tracings collected for the purposes of conventional quantitative EEG analysis must be visually inspected not only to remove artifacts (standard quantitative EEG procedure) but also to examine for abnormal activity and in case such is suspected, a full clinical EEG study would be recommended. Indeed the above line of research has been long neglected despite the

apparent clinical significance.[44] Furthermore, it is expected that by combining EEG biomarkers such as IED, alpha frequency, frontal alpha asymmetry,[13] frontal theta power,[14] and clinical markers, differential prediction of treatment response with clinical relevance might become a reality. In conclusion, EEG abnormalities are associated with nonresponse to escitalopram and venlafaxine-XR, but not sertraline, whereas a slow APF is associated to response to sertraline only.

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Author Contributions

NNB and MA initiated the proposal for this article, which was approved by the iSPOT-D publication committee. NB evaluated all EEG data, MA conducted the statistical analyses and initiated the manuscript. MA, EG, and NB read and contributed to the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following conflicts of interest with respect to the research, authorship, and/or publication of this article: MA reports research grants and options from Brain Resource Ltd (Sydney, Australia), acted as a paid consultant for Bracket, neuroCare group, Mindmedia and Vivatech and is a coinventor on 3 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1) related to EEG, neuromodulation, and psychophysiology, but neither own these nor receives any proceeds related to these patents. EG is founder and receives income as Chief Executive Officer and Chairman for Brain Resource Ltd and has stock options in Brain Resource Ltd. NNB reports no disclosures or conflicts of interest related to this study.

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