Journal of Affective Disorders 259 (2019) 67–72

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Normalization of EEG in depression after antidepressant treatment with sertraline? A preliminary report

N. van der Vinne[a,b,c,*], M.A. Vollebregt[b,d], N.N. Boutros[e], K. Fallahpour[f,g], M.J.A.M. van Putten[c,h,1], M. Arns[b,i,1]

[a] Synaeda Psycho Medisch Centrum, Leeuwarden, the Netherlands
[b] Research Institute Brainclinics, Nijmegen, the Netherlands
[c] Department of Clinical Neurophysiology, Faculty Science and Technology, University of Twente, Enschede, the Netherlands
[d] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands
[e] Saint Luke's Marion Bloch Neuroscience Institute, Kansas City, MO, USA
[f] Icahn School of Medicine, Mount Sinai, New York, USA
[g] Brain Resource Center, New York, USA
[h] Department of Clinical Neurophysiology and Neurology, Medisch Spectrum Twente, Enschede, the Netherlands
[i] Department of Experimental Psychology, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Depression
EEG
Paroxysmal
Antidepressant
Prognosis
Personalized medicine

ABSTRACT

Background: MDD patients with abnormal EEG patterns seem more likely to be non-responsive to the antidepressants escitalopram and venlafaxine, but not sertraline, than patients without EEG abnormalities. This finding suggests that patients with both MDD and abnormal EEGs may differentially respond to antidepressant treatment. In the current study, we investigated whether depressed patients with an abnormal EEG show a normalization of the EEG related to antidepressant treatment and response and whether such effect is drug specific, and whether having had early life stress (ELS) increases the chance of abnormal activity.

Methods: Baseline and week 8 EEGs and depression symptoms were extracted from a large multicenter study (iSPOT-D, $n = 1008$) where depressed patients were randomized to escitalopram, sertraline, or venlafaxine-XR treatment. We calculated Odds Ratios of EEG normalization and depression response in patients with an abnormal EEG at baseline, comparing sertraline versus other antidepressants.

Results: Fifty seven patients with abnormal EEGs were included. EEGs did not normalize significantly more with sertraline compared to other antidepressants (OR = 1.9, $p = .280$). However, patients with a normalized EEG taking sertraline were 5.2 times more likely to respond than subjects taking other antidepressants ($p = .019$). ELS was not significantly related to abnormal activity.

Limitations: Neurophysiological recordings were limited in time (two times 2-minute EEGs) and statistical power ($n = 57$ abnormal EEGs).

Conclusions: Response rates in patients with normalized EEG taking sertraline were significantly larger than in subjects treated with escitalopram/venlafaxine. This adds to personalized medicine and suggests a possible drug repurposing for sertraline.

Introduction

Abnormal activity in the electroencephalogram (EEG) in absence of clinical events (such as seizures) includes paroxysmal activity (e.g. isolated epileptiform discharges (IEDs), intermittent focal slowing) or diffuse slowing of the background pattern. Abnormal EEG activity is not exclusively associated with disorders such as epilepsy and may occur without obvious clinical signs or symptoms. However, it has been hypothesized that particular EEG abnormalities are associated with multiple mental disorders (Boutros, 2018; Inui et al., 1998; Shelley and Trimble, 2009; Yasuhara, 2010), opting the possibility that patients with an abnormal EEG may benefit from medication targeting both the mental disorder and the EEG abnormalities. Assessing pre-treatment EEG abnormalities therefore, could both benefit prognosis reliability

* Corresponding author.
E-mail address: n.van.der.vinne@synaeda.nl (N. van der Vinne).
[1] Shared last authorship.

https://doi.org/10.1016/j.jad.2019.08.016
Received 15 February 2019; Received in revised form 8 August 2019; Accepted 12 August 2019
Available online 13 August 2019

and treatment outcome and would adhere to the standards set by the NIMH with the Research Domain Criteria framework ([RDoC] Insel et al., 2010) under Arousal (Physiology).

EEG abnormalities are reported in 3–5% or patients with MDD, similar to controls (1–6%: Arns et al., 2008; Arns et al., 2017; Goodwin, 1947; Lennox-Buchtal et al., 1960; Monin et al., 2018; Oh et al., 2018; Richter et al., 1971; Shelley et al., 2008). Furthermore, an increased likelihood of developing epilepsy exists in MDD (Kanner et al., 2017). Vice-versa, the most commonly reported psychiatric comorbidity in epilepsy is MDD (Bragatti et al., 2014), as 24% of epileptic patients are affected by MDD (Kanner, 2017).

Ribot et al. (2017) found a decrease in seizure frequency as a result of antidepressant treatment in depressed humans with co-morbid epilepsy. This was irrespective of how well their mood symptoms improved. In animal models, antidepressants (AD) showed a similar decrease in seizure frequency (Kamal, 2007).

Only few studies explored how abnormal EEGs, in the absence of epilepsy, relate to the treatment effects in affective disorders. Arns et al. (2017) showed that a subgroup of MDD patients with abnormal EEG patterns was more likely to be non-responsive to the ADs escitalopram and venlafaxine, whereas response to sertraline was not different for patients with or without EEG abnormalities. These findings suggest that patients with both MDD and abnormal EEGs may differentially respond to AD treatment.

In this light, sertraline might exert some anticonvulsant effects, given the observation that people with abnormal EEGs did respond well to sertraline. This would justify the consideration of repurposing the AD sertraline as a mild anticonvulsant for the treatment of MDD with paroxysmal activity. To explore such repurposing, we studied if sertraline treatment results in more EEG normalization after 8 weeks of treatment, compared to venlafaxine and escitalopram, and if this is associated with clinical response. Sertraline responders were expected to show more normalization than responders to other ADs. This was complemented by evaluating if early life stress (ELS, a potential cause of an abnormal EEG) is associated with abnormal EEG patterns. For background and results, see supplement 1. Our study was not originally designed to detect EEG abnormalities (particularly IEDs) and recordings were limited to 2 min of eyes-open and 2 min of eyes-closed EEG. This is sufficient for detecting slow wave abnormalities (Struve and Boutros, 2005). However, short recordings increase 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 whether normalization after AD treatment occurs in EEGs initially showing abnormalities.

Methods

Design

This study was an international multicenter, randomized, prospective open-label trial (phase IV clinical trial, international Study for Predicting Optimized Treatment in Depression [iSPOT-D]) in which MDD subjects were randomized to escitalopram, sertraline, or venlafaxine-XR treatment in a 1:1:1 ratio. The study protocol details have been published by Saveanu et al. (2015) and Williams et al. (2011).

The iSPOT-D sample consisted of 1008 patients with MDD and 336 healthy controls, the current study focused on 58 subjects having an abnormal EEG (identical to the sample from our previous report, Arns et al., 2017). After excluding data from one subject due to poor EEG quality at endpoint, the sample for our main analyses consisted of 57 patients with MDD displaying an abnormal EEG at baseline measurement. A complete description of the study assessments, inclusion/exclusion criteria, diagnostic procedures, treatment and characterization of this paroxysmal subgroup is available in Arns et al. (2017). In summary, the primary diagnosis of nonpsychotic MDD was confirmed at the baseline visit (before randomization) using the Mini-International Neuropsychiatric Interview (MINI-Plus), according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria, and a score $\geq$16 on the clinician-rated 17-item Hamilton Rating Scale for Depression (HRSD). To measure the neurophysiological consequences of childhood trauma (as was reported in Williams et al., 2016), we used the Early-Life Stress Questionnaire (ELSQ, McFarlane et al., 2005). The ELSQ comprises 18 items, which assess exposure to specific traumatic events in the first 17 years of life (see supplement 2 for the entire questionnaire) and which are equivalent to the trauma items assessed by the Child Abuse and Trauma Scale (Chu et al., 2013; Williams et al., 2016). Each item is scored dichotomously for the presence/absence of exposure to each type of trauma. As reported by Williams et al. (2016), in the complete iSPOT-D sample the extent of exposure to traumatic events was not found to differ across site or across country. All MDD subjects were either AD medication-naive or, if previously prescribed an AD, had undergone a washout period of at least 5 half-lives before the baseline visit clinical and EEG assessments. After the baseline visit, MDD subjects were randomized to 1 of the 3 AD medications. After 8 weeks of treatment, subjects were tested again using the HRSD and EEG, further referred to as endpoint. Subjects provided written informed consent. This study was approved by the local institutional review boards at all the participating sites and was registered at ClinicalTrials.gov (NCT00693849).

Pre and post-treatment assessments

EEG recordings were performed at baseline and at endpoint, using a standardized methodology and platform (Brain Resource Ltd, Australia). Details of this procedure have been published elsewhere (Williams et al., 2011), and details of the reliability and across-site consistency of this EEG procedure have also been published (Paul et al., 2007; Williams et al., 2005). In summary, subjects 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 (NuAmps; 10–20 electrode international system). EEG data were collected for 2 min with eyes open (EO) and 2 min 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 3 mm 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 low-pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization with a sampling rate of 500 Hz.

EEG analysis

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. Data were EOG corrected using a regression-based technique similar to the method described by Gratton et al. (1983). No other artifact rejection was applied to the data other than EOG correction and filtering. Data were visually inspected in Brain Vision Analyzer (Brainproducts, Germany) using a linked ears and queens-square montage. Visual inspection and classification were performed by author N.N.B. (a board-certified electroencephalographer, neurologist, and psychiatrist), who was blinded to the subject's status (patient vs control), clinical data, assessment moment (baseline vs. endpoint) and treatment arm. Details on EEG data analysis and validation can be found elsewhere (Arns et al., 2016). 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 more or less 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, 2014). Supplement 3 contains descriptive and visual information of abnormalities on the individual level. Classification of all abnormalities was in accordance to the guidelines published by the International Federation of Clinical Neurophysiology (Noachtar et al., 1999).

Statistics

Our primary outcome measure was normalization of the EEG, defined as an absence of abnormalities after 8 weeks of AD treatment, for those subjects who were classified as having an abnormal baseline EEG. Treatment response was defined as a more than 50 percent decrease in HRSD score from baseline to endpoint, identical to our previous study. Secondary, we focused on treatment response in patients with a normalized EEG. Differences in age, sex, and depression severity at baseline were tested using 1-way analysis of variance (or nonparametric tests if required). Although pharmacologically different presumed mechanisms of action, we chose to merge escitalopram and venlafaxine groups based on the prior finding that these two drugs show poor clinical response in patients with an abnormal EEG (as opposed to the sertraline group), thereby also equalizing statistical power. For the presence of abnormalities at endpoint, significance level was set at $p \leq 0.05$ and effect sizes of main effects were reported in odds ratios (OR) with 95% confidence intervals (CI). For assessing the relationship between ELS and EEG abnormalities, both ELS in general and abuse in particular, were tested binary (OR with CI) and continuously (summing up all experiences ELS events, testing through logistic regression), for their neurophysiological effect (having an abnormal EEG at baseline or not). Every questionnaire item was also singularly tested binary through the calculation of ORs.

Results

In the abnormal sample, 45% achieved remission (HRSD score below MDD cutoff at endpoint) and 54% reached response to treatment (see Table 1). The number of subjects with an abnormal EEG was significantly higher in the group prescribed with sertraline than other antidepressants, yielding unequal distributions for the number of responders among treatment groups. For the additional ELS analyses, the total sample of patients with complete EEG and ELS data ($n = 1152$) consisted of 878 patients with MDD and 274 healthy controls.

Responders (31.6 ± 10.1 years) did not significantly differ in age (37.3 ± 13.2 years; $p = .065$; $F(1, 56) = 3.535$) or sex ($p = .541$; $\chi^2 = 0.374$) from non-responders. As previously reported (Arns et al., 2017), response rates in this abnormal subgroup were highest in the sertraline group (72%), followed by the other AD group (38%). Based on this sample, escitalopram and venlafaxine were associated with nonresponse in MDD patients with EEG abnormalities, but not so for sertraline. See Table 1 for an overview of response rates.

Drug effect on abnormal EEGs. Out of 57 subjects with an abnormal EEG at baseline, 39 showed no more EEG abnormalities at endpoint (76% after sertraline, 62.5% after another AD). Results are shown in Table 1. Comparing sertraline to the other ADs, OR analyses showed no significant differences in normalization of the EEG at endpoint ($OR = 1.9$, $p = .280$, 95% CI [0.593, 6.084]).

Mediation of EEG normalization on clinical response to different drugs. Responders and non-responders were equally likely to have a normal EEG at endpoint (Table 2). However, when specifically comparing sertraline to other ADs among subjects with a normalized EEG, subjects taking sertraline were 5.2 times more likely to be a responder than subjects taking other ADs ($p = .019$, 95% CI [1.317, 20.539], see Fig. 1). For subjects with an unchanged EEG this difference was not significant ($OR = 2.8$, $p = .325$, 95% CI [0.361, 21.727]).

Early-life stress. Having experienced ELS in general, abuse in general, and specific ELS events in early life, were not related to abnormal EEG. This was the case for 1) the entire iSPOT-D dataset (all ELS data available for MDD patients and controls in the iSPOT-D dataset $n = 1152$, $p \geq .116$), and 2) depressed subjects specifically ($n = 878$, $p \geq .091$): ORs and logistic regression models were non-significant.

Table 2
The number of responders and non-responders in the normal and abnormal endpoint EEG subgroups per treatment and across treatment arms.

		Endpoint normal		Endpoint abnormal	
		n	%*	n	%*
Sertraline	Responders	14	56%	4	16%
	Non-responders	5	20%	2	8%
Other AD	Responders	7	22%	5	16%
	Non-responders	13	40%	7	22%
Venlafaxine	Responders	4	23.5%	3	18%
	Non-responders	6	35%	4	23.5%
Escitalopram	Responders	3	20%	2	13%
	Non-responders	7	47%	3	20%
Total	Responders	21	37%	9	16%
	Non-responders	18	31%	9	16%

* Percentage of the total of all patients belonging to the same treatment arm (both responders and non-responders).

*Percentage of the total of all patients belonging to the same treatment arm (both responders and non-responders)

Discussion

This study aims to extend our observations that depressed patients with an abnormal EEG at baseline are more likely to be a non-responder to venlafaxine or escitalopram, suggesting that sertraline is the preferred treatment in this subgroup (Arns et al., 2017). We investigated whether these patients show both an antidepressant (AD) treatment related and response related temporal change in the EEG and whether

Table 1
Response results after MDD treatment with antidepressants, and EEG outcome at endpoint.

		Response				EEG at endpoint			
	Subgroup total (n)	Responders		Non-responders		Normal		Abnormal	
		n	%	n	%	n	%	n	%
Sertraline	25	18	72%	7	28%	19	76%	6	24%
Other AD	32	12	37.5%	20	62.5%	20	62.5%	12	37.5%
Venlafaxine	17	7	41%	10	59%	10	59%	7	41%
Escitalopram	15	5	33%	10	67%	10	67%	5	33%
Total	57	30	53%	27	47%	39	68%	18	32%

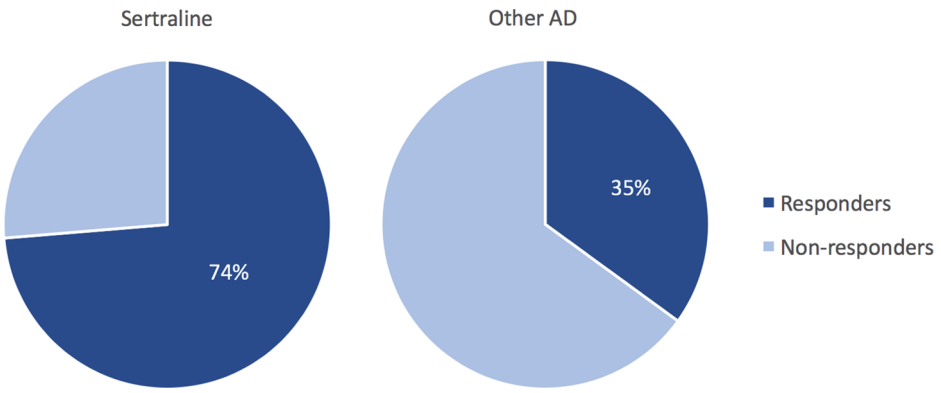

Fig. 1. Treatment response for subjects with a normalized EEG at endpoint, per AD type (sertraline $n = 19$, other AD $n = 20$). Percentages indicate response within each respective AD type.

early life stress (ELS) increases the chance of observing abnormal EEG activity. We show that EEG normalization patterns – rated blind to diagnosis and treatment – did not significantly differ between sertraline and other AD treatment for 8 weeks. However, when comparing sertraline treatment to the other ADs within the subjects who had a normalized EEG at endpoint, response was more likely to be achieved with sertraline than with other treatments. A mediating effect of ELS in developing an abnormal EEG (with ELS increasing the chance of such an EEG) was neither found in the whole sample of controls and depressed, nor in the depressed subsample.

To the best of our knowledge, this is the first study to explore the effects of ADs on abnormal EEGs of depressed patients. Several research groups did study the effects of a range of ADs on seizures (including sertraline), finding no adverse influence on seizure frequency (Hovorka et al., 2000; Kanner et al., 2000; Maguire et al., 2014; Okazaki et al., 2011; Thomé-Souza et al., 2007). Moreover, beneficial treatment effects of selective serotonin (and norepinephrine) reuptake inhibitors (SSRIs and SNRIs) on patients with epilepsy have been published before (Alper et al., 2007; Favale et al., 2003; Hamid and Kanner, 2013; Kanner, 2016; Specchio et al., 2004). Abnormal EEGs however, were not subject to such investigations before. Our results suggest that depression response with concurrent EEG normalization occurs more often after sertraline treatment than escitalopram or venlafaxine. Note that this entails an assessment of abnormalities normally deemed subclinical by neurologists. Our inconclusive findings on ELS (whole sample $n = 1152$ and MDD sample $n = 878$) provided no additional clarification that would help elucidate underlying mechanisms involved in both developing MDD and displaying an abnormal EEG (see supplement 1 for background and results).

Remarkable is the differential effect of sertraline in terms of treatment response, compared to escitalopram and venlafaxine in subjects who had a normalized EEG, which was discussed before (Arns et al., 2017). Only escitalopram also acts on the allosteric sites of the serotonin transporter and has higher selectivity for this transporter. Sertraline on the other hand, has the most pronounced dopamine active transporter inhibitory activity (Sanchez et al., 2014). However, new literature on the different antidepressant profiles has barely clarified how this might have consequential effects on the (abnormal) human EEG. In a rodent model, sertraline prevented or diminished induced seizures (presumably mostly through effective inhibition of brain presynaptic Na+ channel permeability), comparable to antiepileptic drug carbamazepine (Sitges et al., 2012). Kanekar et al. (2018) did suggest a differential working mechanism in sertraline compared to other ADs, considering the increased inhibition of dopamine active transporter by sertraline. According to Bozzi and Borelli (2013), altered D2R signaling (part of the dopamine system), leading to decreased D2R function, might be involved in epileptogenesis, adding to earlier findings that dopamine plays a role in juvenile myoclone epilepsy and general tonic clonic seizures (Ciumas et al., 2010; Ciumas et al., 2008). Although the generalization of our results on EEG abnormalities to epileptogenesis is uncertain, it might help explain in part how EEG abnormalities in depressed patients are best treated with sertraline, but further research is necessary to understand the mechanisms that may be underlying the differential effects of treatments.

Limitations

As the frequency of IEDs is highly variable and in part modulated by sleep (Askamp and van Putten, 2014; Geut et al., 2017), our short EEG recordings will have limited sensitivity to detect IEDs (Boutros, 2018). However, the most observed abnormalities in this sample, diffuse and focal slow activity, have a relatively high chance of being observed in one recording session as these findings are relatively stationary. Another limitation is that all EEG epochs were assessed by visual analysis. While this is still the gold standard for detection of paroxysms, global features (e.g. mean frequency) may be assessed more reliably with quantitative EEG. Further, we did not assess spontaneous fluctuations in these findings, nor differentiate between the different types of abnormalities (different types of IEDs and slowing).

In the search of treatment optimization, future studies involving larger samples (e.g. from consortia) allow for investigating whether the degree of abnormality is indicative of the chance of treatment success. New methods in neuroscience such as deep learning, could assist in this quest (Tjepkema-Cloostermans et al., 2018) as well as using a multimodal and integrative approach where data from various domains is combined in order to optimize prediction, including cognitive, psychological and genetic information (e.g. Spronk et al., 2011). For future similar studies, we propose that records are interpreted by two independent EEG specialists, both blinded to group and treatment. Possible changes in EEG of participants that showed no abnormalities at baseline have not been investigated in the current study. This may, however, help explain the normalization of EEG after treatment or lack thereof. Findings from Sitges et al. (2012) imply that EEG normalization could occur after sertraline treatment, irrespective of treatment response. As our findings were not based on the ratio of normalization in responders and non-responders, future studies could further investigate EEG normalization of sertraline irrespective of response status. Future studies should also address the relation between duration of the EEG and likelihood of detection of paroxysms to define the optimal recording time within practical limits. Although in previous epileptiform EEG studies SSRIs and SNRIs have been discussed as a treatment in general, our results show the importance to discriminate between specific ADs and incorporate several ADs within one study.

In conclusion, albeit in a small sample, our data demonstrate that patients showing a normalized EEG after MDD treatment comprised of more sertraline responders, than responders to escitalopram or

venlafaxine. This first exploration of the relationship between EEG paroxysms and MDD treatment response points towards the suggestion that differentiation within a psychiatric patient group that seems homogenous at first (with respect to its symptoms), may improve treatment efficacy. To this end, a more routinely use of EEG in psychiatry could assist in personalized medicine.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

N. van der Vinne: Conceptualization, Formal analysis, Writing - original draft. **M.A. Vollebregt:** Conceptualization, Formal analysis, Writing - original draft. **N.N. Boutros:** Conceptualization, Funding acquisition, Formal analysis, Writing - review & editing. **K. Fallahpour:** Conceptualization, Funding acquisition. **M.J.A.M. van Putten:** Conceptualization, Formal analysis, Writing - review & editing. **M. Arns:** Conceptualization, Funding acquisition, Formal analysis, Writing - original draft.

Declaration of Competing Interest

NvdV, MV, NNB and KF report no relevant financial disclosures. MvP is a co-founder of Clinical Science Systems. MA reports options from Brain Resource (Sydney, Australia); he is director and owner of Research Institute Brainclinics, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on four 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 funding from Brain Resource (Sydney, Australia) and neuroCare Group (Munich, Germany), however data analyses and writing of this manuscript were unconstrained.

Acknowledgements

We acknowledge the iSPOT-D Investigators Group, the contributions of iSPOT-D principal investigators at each site, the central management team (global coordinator Claire Day).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.08.016.

References

Alper, K., Schwartz, K.A., Kolts, R.L., Khan, A., 2007. Seizure incidence in psychopharmacological clinical trials: an analysis of food and drug administration (FDA) summary basis of approval reports. Biol. Psychiatry 62 (4), 345–354. https://doi.org/10.1016/j.biopsych.2006.09.023.

Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D.M., Etkin, A., ... Gordon, E., 2016. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized ispot-d study. Clin. Neurophysiol. 127, 509–519. http://dx.doi.org/10.1016/j.clinph.2015.05.032.

Arns, M., Gordon, E., Boutros, N.N., 2017. EEG abnormalities are associated with poorer depressive symptom outcomes with escitalopram and venlafaxine-xr, but not sertraline: results from the multicenter randomized ispot-d study. Clin. EEG Neurosci. 48 (1), 33–40. https://doi.org/10.1177/1550059415621435.

Arns, M., Gunkelman, J., Breteler, M., Spronk, D., 2008. EEG phenotypes predict treatment outcome to stimulants in children with ADHD. J. Integr. Neurosci. 7 (3), 421–438. https://doi.org/10.1142/s0219635208001897.

Askamp, J., van Putten, M., 2014. Mobile EEG in epilepsy. Int. J. Psychophysiol. 91, 30–35. https://doi.org/10.1016/j.ijpsycho.2013.09.002.

Boutros, N.N., 2014. Standard EEG: A Research Roadmap for Neuropsychiatry. Springer.

Boutros, N.N., 2018. The forsaking of the clinical EEG by psychiatry: how justified? CNS Spectr. 23 (3), 196–204. https://doi.org/10.1017/S1092852917000505.

Bozzi, Y., Borrelli, E., 2013. The role of dopamine signaling in epileptogenesis. Front. Cell Neurosci. 7, 157. https://doi.org/10.3389/fncel.2013.00157.

Bragatti, J.A., Torres, C.M., Cherubini, P.A., Leistner-Segal, S., Bianchin, M.M., 2014. Is interictal EEG activity a biomarker for mood disorders in temporal lobe epilepsy? Clin. Neurophysiol. 125 (10), 1952–1958. https://doi.org/10.1016/j.clinph.2014.02.013.

Chu, D.A., Williams, L.M., Harris, A.W.F., Bryant, R.A., Gatt, J.M., 2013. Early life trauma predicts self-reported levels of depressive and anxiety symptoms in nonclinical community adults: relative contributions of early life stressor types and adult trauma exposure. J. Psychiatr. Res. 47 (1), 23–32. https://doi.org/10.1016/j.jpsychires.2012.08.006.

Ciumas, C., Wahlin, T.-B.R., Espino, C., Savic, I., 2010. The dopamine system in idiopathic generalized epilepsies: identification of syndrome-related changes. Neuroimage 51 (2), 606–615. https://doi.org/10.1016/j.neuroimage.2010.02.051.

Ciumas, C., Wahlin, T.-B.R., Jucaite, A., Lindstrom, P., Halldin, C., Savic, I., 2008. Reduced dopamine transporter binding in patients with juvenile myoclonic epilepsy. Neurology 71 (11), 788–794. https://doi.org/10.1212/01.wnl.0000316120.70504.d5.

Favale, E., Audenino, D., Cocito, L., Albano, C., 2003. The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis. Seizure 12 (5), 316–318. https://doi.org/10.1016/S1059-1311(02)00315-1.

Geut, I., Knottnerus, I.L.H., van Putten, M.J.A.M., 2017. Detecting interictal discharges in first seizure patients: ambulatory EEG or EEG after sleep deprivation? Seizure 51, 52–54. https://doi.org/10.1016/j.seizure.2017.07.019.

Goodwin, J.E., 1947. The significance of alpha variants in the EEG, and their relationship to an epileptiform syndrome. Am. J. Psychiatry 104 (6), 369–379.

Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. Electroencephalogr. Clin. Neurophysiol. 55 (4), 468–484.

Hamid, H., Kanner, A.M., 2013. Should antidepressant drugs of the selective serotonin reuptake inhibitor family be tested as antiepileptic drugs? Epilepsy Behav. 26 (3), 261–265. https://doi.org/10.1016/j.yebeh.2012.10.009.

Hovorka, J., Herman, E., Nemcová, 2000. Treatment of interictal depression with citalopram in patients with epilepsy. Epilepsy Behav. 1 (6), 444–447. https://doi.org/10.1006/ebeh.2000.0123.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., ... Wang, P., 2010. Research domain criteria (rdoc): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167 (7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379.

Inui, K., Motomura, E., Okushima, R., Kaige, H., Inoue, K., Nomura, J., 1998. Electroencephalographic findings in patients with DSM-IV mood disorder, schizophrenia, and other psychotic disorders. Biol. Psychiatry 43 (1), 69–75. https://doi.org/10.1016/S0006-3223(97)00224-2.

Kamal, S.M., 2007. Effect of escitalopram and venlafaxine on seizure score and lipid peroxidation in mice receiving carbamazepine antiepileptic therapy. J. Egypt Soc. Toxicol. 36, 1–6.

Kanekar, S., Sheth, C.S., Ombach, H.J., Olson, P.R., Bogdanova, O.V., Petersen, M., ... Renshaw, P.F., 2018. Hypobaric hypoxia exposure in rats differentially alters antidepressant efficacy of the selective serotonin reuptake inhibitors fluoxetine, paroxetine, escitalopram and sertraline. Pharmacol. Biochem. Behav. 170, 25–35. https://doi.org/10.1016/j.pbb.2018.05.002.

Kanner, A.M., 2016. Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: a review of the evidence. Epilepsy Behav. 61, 282–286. https://doi.org/10.1016/j.yebeh.2016.03.022.

Kanner, A.M., 2017. Psychiatric comorbidities in new onset epilepsy: should they be always investigated. Seizure 49, 79–82. https://doi.org/10.1016/j.seizure.2017.04.007.

Kanner, A.M., Kozak, A.M., Frey, M., 2000. The use of sertraline in patients with epilepsy: is it safe. Epilepsy Behav. 1 (2), 100–105. https://doi.org/10.1006/ebeh.2000.0050.

Kanner, A.M., Scharfman, H., Jette, N., Anagnostou, E., Bernard, C., Camfield, C., ... Pohlmann-Eden, B., 2017. Epilepsy as a network disorder (1): what can we learn from other network disorders such as autistic spectrum disorder and mood disorders? Epilepsy Behav. 77, 106–113. https://doi.org/10.1016/j.yebeh.2017.09.014.

Krauss, G.L., Fisher, R.S., Kaplan, P.W., 2010. The Johns Hopkins Atlas of Digital EEG : An Interactive Training Guide. Johns Hopkins University Press, Baltimore.

Lennox-Buchtal, M., Buchtal, F., Rosenfalck, P., 1960. Correlation of electroencephalographic findings with crash rate of military jet pilots. Epilepsia 1, 366–372.

Maguire, M.J., Weston, J., Singh, J., Marson, A.G., 2014. Antidepressants for people with epilepsy and depression. Cochrane Database System. Rev.(12). https://doi.org/10.1002/14651858.CD010682.pub2.

McFarlane, A., Clark, C.R., Bryant, R.A., Williams, L.M., Niaura, R., Paul, R.H., ... Gordon, E., 2005. The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. J. Integr. Neurosci. 4 (1), 27–40. https://doi.org/10.1142/S0219635205000689.

Monin, J., Pruvost-Robieux, E., Huiban, N., Marchi, A., Crepon, B., Dubourdieu, D., ... Gavaret, M., 2018. Prevalence of benign epileptiform variants during initial EEG examination in french military aircrew. Neurophysiol. Clin. 48 (3), 171–179. https://doi.org/10.1016/j.neucli.2018.04.001.

Niedermeyer, E., 2005. Abnormal EEG patterns: epileptic and paroxysmal. In: Lopes Da Silva, F. (Ed.), Electroencephalography: Basic Principles, Clinical Applications, and Related Fields, 5th ed. Lippincott Williams & Wilkins, Baltimore, pp. 255–280.

Noachtar, S., Binnie, C., Ebersole, J., Mauguière, F., Sakamoto, A., Westmoreland, B., 1999. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The international federation of clinical neurophysiology. Electroencephalogr. Clin. Neurophysiol. Suppl. 52, 21–41.

Oh, D.A., Kim, H., Bae, E.K., 2018. Electroencephalographic abnormalities in the screening for pilot applicants in Korea. J. Clin. Neurol. 14 (2), 212–214. https://doi.

org/10.3988/jcn.2018.14.2.212.
Okazaki, M., Adachi, N., Ito, M., Watanabe, M., Watanabe, Y., Kato, M., Onuma, T., 2011. One-year seizure prognosis in epilepsy patients treated with antidepressants. Epilepsy Behav. 22 (2), 331–335. https://doi.org/10.1016/j.yebeh.2011.07.016.
Paul, R.H., Gunstad, J., Cooper, N., Williams, L.M., Clark, C.R., Cohen, R.A., ... Gordon, E., 2007. Cross-cultural assessment of neuropsychological performance and electrical brain function measures: additional validation of an international brain database. Int. J. Neurosci. 117 (4), 549–568. https://doi.org/10.1080/00207450600773665.
Ribot, R., Ouyang, B., Kanner, A.M., 2017. The impact of antidepressants on seizure frequency and depressive and anxiety disorders of patients with epilepsy: is it worth investigating? Epilepsy Behav. 70 (Pt A), 5–9. https://doi.org/10.1016/j.yebeh.2017.02.032.
Richter, P.L., Zimmerman, E.A., Raichle, M.E., Liske, E., 1971. Electroencephalograms of 2947 United States air force academy cadets (1965-1969). Aerosp. Med. 42 (9), 1011–1014.
Sanchez, C., Reines, E.H., Montgomery, S.A., 2014. A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? Int. Clin. Psychopharmacol. 29 (4), 185–196. https://doi.org/10.1097/YIC.0000000000000023.
Saveanu, R., Etkin, A., Duchemin, A.-M., Goldstein-Piekarski, A., Gyurak, A., Debattista, C., ... Williams, L.M., 2015. The international study to predict optimized treatment in depression (ispot-d): outcomes from the acute phase of antidepressant treatment. J. Psychiatr. Res. https://doi.org/10.1016/j.jpsychires.2014.12.018.
Sharbrough, F.W., 2005. Nonspecific abnormal EEG patterns. In: Niedermeyer, E., Lopes Da Silva, F. (Eds.), Electroencephalography: Basic Principles, Clinical Applications, and Related Fields, 5th ed. Lippincott Williams & Wilkins, Baltimore, pp. 235–254.
Shelley, B.P., Trimble, M.R., 2009. "All that spikes is not fits", mistaking the woods for the trees: the interictal spikes–an "EEG chameleon" in the interface disorders of brain and mind: a critical review. Clin. EEG Neurosci. 40 (4), 245–261. https://doi.org/10.1177/155005940904000407.
Shelley, B.P., Trimble, M.R., Boutros, N.N., 2008. Electroencephalographic cerebral dysrhythmic abnormalities in the trinity of nonepileptic general population, neuropsychiatric, and neurobehavioral disorders. J. Neuropsychiatry Clin. Neurosci. 20 (1), 7–22. https://doi.org/10.1176/appi.neuropsych.20.1.7.
Sitges, M., Aldana, B.I., Gómez, C.D., Nekrassov, V., 2012. The antidepressant sertraline prevents the behavioral and eeg changes induced in two animal models of seizures. Epilepsy Behav. 25 (4), 511–516. https://doi.org/10.1016/j.yebeh.2012.09.005.
Specchio, L.M., Iudice, A., Specchio, N., La Neve, A., Spinelli, A., Galli, R., ... Murri, L., 2004. Citalopram as treatment of depression in patients with epilepsy. Clin. Neuropharmacol. 27 (3), 133–136.
Spronk, D., Arns, M., Barnett, K.J., Cooper, N.J., Gordon, E., 2011. An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: a pilot study. J. Affect. Disord. 128 (1–2), 41–48. https://doi.org/10.1016/j.jad.2010.06.021.
Struve, F.A., Boutros, N.N., 2005. Somatic implications of generalized and/or focal EEG slowing in psychiatric patients. Clin. EEG Neurosci. 36 (3), 171–175.
Thomé-Souza, M.S., Kuczynski, E., Valente, K.D., 2007. Sertraline and fluoxetine: safe treatments for children and adolescents with epilepsy and depression. Epilepsy Behav. 10 (3), 417–425. https://doi.org/10.1016/j.yebeh.2007.01.004.
Tjepkema-Cloostermans, M.C., de Carvalho, R.C.V., van Putten, M.J.A.M., 2018. Deep learning for detection of focal epileptiform discharges from scalp EEG recordings. Clin. Neurophysiol. 129 (10), 2191–2196. https://doi.org/10.1016/j.clinph.2018.06.024.
Williams, L.M., Debattista, C., Duchemin, A.-M., Schatzberg, A.F., Nemeroff, C.B., 2016. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. Transl. Psychiatry 6, e799. https://doi.org/10.1038/tp.2016.61.
Williams, L.M., Rush, A.J., Koslow, S.H., Wisniewski, S.R., Cooper, N.J., Nemeroff, C.B., ... Gordon, E., 2011. International study to predict optimized treatment for depression (ispot-d), a randomized clinical trial: rationale and protocol. Trials 12, 4. https://doi.org/10.1186/1745-6215-12-4.
Williams, L.M., Simms, E., Clark, C.R., Paul, R.H., Rowe, D., Gordon, E., 2005. The test-retest reliability of a standardized neurocognitive and neurophysiological test battery: "Neuromarker. Int. J. Neurosci. 115 (12), 1605–1630. https://doi.org/10.1080/00207450590958475.
Yasuhara, A., 2010. Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). Brain Dev. 32 (10), 791–798. https://doi.org/10.1016/j.braindev.2010.08.010.