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EEG abnormalities are not associated with poor antidepressant treatment outcome - A NeuroPharm study

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ABSTRACT

EEG brain abnormalities, such as slowing and isolated epileptiform discharges (IEDs), has previously been associated with non-response to antidepressant treatment with escitalopram and venlafaxine, suggesting a potential need for treatment with anticonvulsant property in some patients. The current study aims to replicate the reported association of EEG abnormality and treatment outcomes in an open-label trial of escitalopram for major depressive disorder (MDD) and explore its relationship to mood and cognition. Pretreatment, 6 min eyes-closed resting-state 256-channel EEG was recorded in 91 patients with MDD (age 18–57) who were treated with 10–20 mg escitalopram for 12 weeks; patients could switch to duloxetine after four weeks. A certified clinical neurophysiologist rated the EEGs.

IED and EEG slowing was seen in 13.2%, and in 6.6% there were findings with unclear significance (i.e., Wicket spikes and theta activity). We saw no group-difference in remission or response rates after 8 and 12 weeks of treatment or switching to duloxetine. Patients with EEG abnormalities had higher pretreatment mood disturbances driven by greater anger (p = .039) and poorer verbal memory (p = .012). However, EEG abnormality was not associated with improved mood or verbal memory after treatment. Our findings should be interpreted in light of the rarity of EEG abnormalities and the sample size. While we cannot confirm that EEG abnormalities are associated with non-response to treatment, including escitalopram, abnormal EEG activity is associated with poor mood and verbal memory. The clinical utility of EEG abnormality in antidepressant treatment selection needs careful evaluation before deciding if useful for clinical implementation.

1. Introduction

Depression is a complex and prevalent mental illness that remains difficult to treat efficiently despite several available antidepressant options. Unfortunately, first-line antidepressants such as selective serotonin reuptake inhibitors (SSRIs) fail to facilitate remission in most patients with major depressive disorder (MDD) (Rush et al., 2006). There is no clear evidence-based strategy for medication when patients inadequately respond to several antidepressants. This has led to a search for predictive markers of treatment response to guide treatment selection and provide precision psychiatric care.

Electroencephalography (EEG) is a cost-effective and scalable clinical tool that has shown promise for predicting treatment outcomes (Olbrich and Arns, 2013), but is limited by underreporting of negative results and a lack of out-of-sample validation and replication of previous findings (Widge et al., 2019). For example, research based on data from the international Study to Predict Optimized Treatment in Depression (iSPOT-D) suggests that in patients with depression, abnormality EEG activity such as isolated epileptiform discharges (IEDs) and EEG slowing is a biomarker for non-response to escitalopram and venlafaxine but not
The conventional view is that the slowing of EEG rhythms and the presence of IEDs indicate different pathological processes (Markand, 2003). EEG slowing refers to a decrease in the frequency of the electrical activity. It can be seen in a variety of conditions, including brain injury, neurological disorders, and certain medications. But can also occur naturally during sleep or states of relaxation or meditation. IEDs are abnormal electrical discharges that indicate a hyperexcitable state of the brain. Although interictal epileptiform discharges are typically found in patients with epilepsy, isolated epileptiform discharges are also found in other brain disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder (Swatzyna et al., 2016). However, their association with affective disorders such as MDD and anxiety is not well understood. Previous studies suggest an incidence of 3–5% in MDD (Shelley et al., 2019), similar to the 1–6% prevalence of paroxysmal EEG in normal adult populations (Pietrucha et al., 2010; Okubo et al., 1994; Richter et al., 1971; Shelley et al., 2008). A couple of studies suggest that the prevalence of EEG abnormalities in patients with MDD is approximately 10–17% (Arns et al., 2015; Vinne et al., 2021), similar when compared to healthy controls (Arns et al., 2015).

Abnormal EEG activity has been associated with poorer cognitive function (Meghdadi et al., 2021), and patients with panic disorder and epileptiform activity have been found to respond clinically to antidepressants (McNamara and Fogel, 1990). Additionally, the antiepileptic drug lamotrigine is used as a mood stabilizer and antidepresant in bipolar affective disorder. Rodent studies also suggest that SSRIs, such as fluoxetine in low and moderate doses, have an anticonvulsant effect (Aygun, 2019). Sertraline is also suggested to normalize IEDs due to a possible dopaminergic action (Vinne et al., 2019). In contrast, the antipsychotic clozapine is clinically known to frequently induce EEG slowing and epileptiform discharges (Jackson and Seneviratne, 2019). Thus, the role of IEDs in depression, its associations with anxiety and cognitive dysfunction, and its treatment effects are not well understood.

We here seek to replicate the putative associations of abnormal EEG activity and treatment outcome, to mood, anxiety, and cognition, in an independent cohort from an open-label 12-week study of escitalopram treatment with close clinical follow-up in MDD (Köhler-Forsberg et al., 2020). Our primary research question is whether the presence of EEG abnormalities is associated with poorer response to serotonergic treatment and, secondarily, whether this association EEG abnormalities are associated with differences in mood, anxiety, or cognitive function.

2. Materials and methods

We report findings from the NeuroPharm study, a longitudinal, open-label multimodal neuroimaging clinical trial investigating potential biomarkers in the antidepressant treatment of MDD. The NeuroPharm-I study was approved by the Ethics committee for the Capital Region of Copenhagen (protocol: H-15017713) and was pre-registered at www.clinicaltrials.gov (reg. nr. NCT02869035). For a detailed protocol description, see Köhler-Forsberg et al., 2020.

2.1. Subjects and treatment

Non-psychotic antidepressant-free patients, 18–65 years of age, suffering from a moderate to severe depressive episode lasting less than two years were assessed for inclusion in the study. Patients were eligible if they had been free of antidepressant medication for >2 months, had not previously exhibited non-response to SSRIs, and had not undergone more than one antidepressant treatment attempt in the current depressive episode. Patients were recruited through their primary care centre or a central referral site at the Mental Health Services of the Capital Region of Copenhagen. MDD diagnosis was confirmed by certified psychiatrists and corroborated by a Mini-International Neuropsychiatric Interview (MINI) version 6 (Sheehan et al., 1998). The detail inclusion and exclusion criteria are listed in Köhler-Forsberg et al., 2020. Briefly, patients were screened for and excluded neurological or substance or alcohol use disorders, the use of any CNS drug that could not be washed out prior to participation (e.g., metoclopramide, ondansetron, serotoninergic migraine medicine, clonidine, antiepileptic medication); a history of brain injury (i.e., loss of consciousness and amnesia or symptoms of concussion disorder), or medical conditions interfering with measurements (e.g., epilepsy).

Ninety-one patients with MDD completed the pretreatment investment program, and 86 patients started antidepressant treatment with escitalopram, individually adjusted to 10–20 mg daily depending on response and side effects. In addition, per standard practice, patients experiencing intolerable side effects or <25% reduction in HAMD, from pretreatment at week four were offered to switch to the serotonin-norepinephrine reuptake inhibitor (SNRI), duloxetine (n = 17), individually adjusted (30–120 mg daily). Treatment adherence was assessed by plasma levels of medication at week 8. See supplementary figure S1 for the CONSORT diagram.

2.2. Depression severity and treatment response

Depression symptom severity was assessed with the Hamilton Depression Rating Scale (HAMD<sub>17</sub>) interview before and at weeks 4, 8, and 12 of treatment. Treatment responder was defined as > 50% improvement in ΔHAMD<sub>17</sub> (from pretreatment to week 8) or else patients were defined as non-responders. In the NeuroPharm trial, we also use the 6-item subscale (HAMD<sub>6</sub>) to assess the treatment effect because HAMD<sub>6</sub> captures core depressive symptoms and is more sensitive to antidepressant treatment response (Østergaard et al., 2016; Timmerby et al., 2017).

2.3. Mood disturbance and anxiety

Mood disturbance was assessed by the Profile of Mood States (POMS) as the Total Mood Disturbance (TMD) based on the six mood states—Tension-Anxiety, Anger-Hostility, Vigor, Fatigue-Inertia, Depression-Dejection, Confusion-Bewildernent. Anxiety was assessed pretreatment by the 10-item Generalized Anxiety Disorder (GAD-10) scale (Bech et al., 2005).

2.4. Working memory and verbal memory

Trained neuropsychologists conducted testing in standardised test rooms before drug intervention.

The Letter Number Sequence (LNS) task assessed working memory capacity (Wechsler, 1997). One outlier from the LNS task was excluded as the patient had misunderstood the test instructions.

The Verbal Affective Memory Task 26 (VAMT-26) was used to assess the learning and recall of affective words (Dam et al., 2020; Hjordt et al., 2020). Here, total word recall, calculated as the average number of words (positive, negative, and neutral) recalled across immediate, short-term, and long-term recall in the VAMT-26, was used to assess explicit non-affective verbal memory function.

Affective memory bias was calculated by subtracting negative word scores from positive word scores.

2.5. EEG recording

Patients were seated in a comfortable armchair in a quiet room. Resting EEG was recorded with both eyes closed and open. Participants were instructed to remain quiet and relaxed, avoid eye blinks and movements, and relax chin muscles during recording. Resting EEG was...
recorded during four 3 min periods with a counterbalanced order of COCOC (O for eyes open, C for eyes closed) or COCOC between subjects. EEG data were recorded using a 256-channel HydroCel Sensor Net system (EGI, Inc., Eugene, OR) at 1000 Hz with 0.1–100 Hz analog filtering, the vertex electrode served as the reference channel. Impedances were kept <50 kΩ during the recording.

2.6. EEG classification

Only eyes-closed EEG data were included in the analysis. A board-certified neurophysiologist (O.U.C.) visually inspected the EEGs, blinded to patients’ clinical data. The abnormal EEG activity was rated according to international guidelines (Kane et al., 2017) to identify the prevalent posterior rhythmic activity, which included alpha peak frequency (APF) and background. Moreover, interictal activity was evaluated and categorized as either focal or generalized, which entailed EEG slowing or potential epileptiform activity. The diffuse slowing manifested when the background frequency persistently remained below the alpha range (α, 8–13 Hz). Conversely, focal slowing occurred if rhythms slower than alpha, such as theta (θ, 4–7.9 Hz) or delta (δ, 0.5–3.9 Hz), were continually detected in a particular region.

Epileptiform or paroxysmal activities refer to any EEG pattern emerging and disappearing paradoxically from ongoing background activity (Grant et al., 2014). In contrast, non-paroxysmal slow wave activities of both focal and generalized types existed frequently with some waxing and waning - note that records persisted mostly to fully awake subjects. Finally, controversial waveforms such as Wicket spikes (single waveforms that occur in brief trains or clusters) were also scored. These waveforms are paroxysmal but are of uncertain significance.

2.7. Statistics

We compared features between the unmedicated MDD patients with and without EEG abnormality using Welch’s t-test and Fisher’s exact test, and ANCOVAs to adjust for age and sex. To identify the primary mood disturbance in the Total Mood Disturbance from POMS, we used logistic regression with EEG abnormality as the dependent variable and POMS subscales, with age and sex as covariates.

We used Fisher’s exact test to assess the frequency of EEG abnormality in clinical groups i.e., treatment responders and non-responders.

To assess clinical, mood, and cognitive changes during treatment, we used repeated measures ANCOVA with age and sex. In addition, to align with the prior study (Arns et al., 2015), we performed partial correlations conditioned on age between APF and the percentage improvement in the HAMD17 at week 8. The change in prevalence in EEG abnormality during treatment was assessed with McNemar chi-square.

We present the estimates with 95% confidence intervals (CI) and p-values unadjusted for multiple comparisons. Greenhouse-Geisser correction was used when the sphericity assumption for ANOVAs was not met. Effect sizes are given in Cohen’s d and omega-squared (ω²). The significant level was set to 0.05. Statistics were done in JASP version 0.17.1 (JASP-team, 2023).

3. Results

3.1. Sociodemographic and clinical characteristics

Abnormal EEG findings were present in 20% of the patients (n=18): 13% had IED and EEG slowing, and 7% had other findings with unclear significance (Wicket spikes and theta activity, Table 1, supplementary Figure S2). The abnormal activity was predominately located in the frontotemporal regions and mostly bilateral. The demographics and other clinical profiles of patients with and without EEG abnormalities were not significantly different (p-values >0.11, Table 2), except patients with EEG abnormalities had a borderline significant higher self-reported total mood disturbance (t(89)=1.92, Cohen’s d=0.51, p=0.058). Patients with EEG abnormalities did not have greater familial disposition for affective disorders (p=0.81, Table 2). One patient in our study was undergoing treatment with disulfiram to prevent a relapse of alcoholism, and another patient had a history of migraines but did not use sumatriptan during the study period. Importantly, neither of the patients exhibited EEG abnormalities. The rest of the participants did not have any history of neurological disorders or substance use disorders.

3.2. EEG abnormality and treatment effects on depression and mood

The remission and response rates were not significantly different between groups with and without EEG abnormality at 8 or 12 weeks of antidepressant treatment, nor was the rate of switching to duloxetine

### Table 1

<table>
<thead>
<tr>
<th>EEG abnormality</th>
<th>Pretreatment (n=91)</th>
<th>Week 8 (per-protocol analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder* (n=42)</td>
<td>Non-responder (n=38)</td>
</tr>
<tr>
<td>Isolated epileptiform</td>
<td>6.6%</td>
<td>7.1%</td>
</tr>
<tr>
<td>- Sharp and slow waves</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>EEG slowing</td>
<td>6.6%</td>
<td>7.1%</td>
</tr>
<tr>
<td>- Only slow waves</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Abnormality with unclear significance</td>
<td>6.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>- Wicket spikes and theta activity</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

91 EEG were assessed.

* Clinical response was defined using relative HAMD17 scores from week 8 to pretreatment, with Responders having a >50% improvement. One patient was not assessed at week 8, but was assessed at week 12 as a non-responder and is included as a non-responder at week 8. The frequency of EEG abnormality was not significantly different between treatment responders and non-responders at week 8 (Fisher’s exact test, Odds ratio=0.94 CI: 0.23; 3.65, p=1.00).

### Table 2

Demographic and clinical profile.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No abnormality (n=73)</th>
<th>With abnormality (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.8 (18.6–57.3)</td>
<td>19.0–44.4</td>
</tr>
<tr>
<td>Education scorea</td>
<td>15.1 (2.2)</td>
<td>14.2 (2.0)</td>
</tr>
<tr>
<td>Clinical</td>
<td>Single/Recurrent episode</td>
<td>32/41 (44/56%)</td>
</tr>
<tr>
<td>1st-degree disposition scorea</td>
<td>1.3 (1.5)</td>
<td>1.2 (1.2)</td>
</tr>
<tr>
<td>HAMD17</td>
<td>22.9 (3.4)</td>
<td>22.7 (3.4)</td>
</tr>
<tr>
<td>HAMDb</td>
<td>12.3 (1.7)</td>
<td>12.4 (1.5)</td>
</tr>
<tr>
<td>TMD</td>
<td>80.7 (31.8)</td>
<td>96.7 (31.5)</td>
</tr>
<tr>
<td>GAD-10c</td>
<td>23.6 (9.9)</td>
<td>26.9 (8.1)</td>
</tr>
</tbody>
</table>

MDD: Major Depressive Disorder. aEducation level and disposition based on first-degree relatives were only available for 61 without and 13 with EEG abnormality. bInformation on episode was not available for one participant with EEG abnormality. cGAD-10, a self-report of anxiety during the previous two weeks, was only available for 71 without and 15 with EEG abnormality. TMD: Total Mood Disturbance measured by Profile of Moods. HAMD17: 17-item Hamilton Depression Rating scale. HAMDb: 6-item subscale. P-values calculated by student’s t-tests and *Fishers exact test.
A repeated ANOVA with age and sex as covariates was performed to compare the effect of EEG abnormality on depression severity at 4, 8, and 12 weeks of treatment, where EEG abnormality did not interact with changes in severity assessed by HAMD_{17} (F(3216) = 0.09, \( \omega^2 = 0.00, p = .95 \)) or HAMD_{6} (F(3216) = 0.36, \( \omega^2 = 0.00, p = .79 \)). Removing the four patients (one with abnormal EEG activity) deemed non-adherent to treatment from analyses did not change the findings.

Similar to a prior study (Arns et al., 2015), we also observed a non-significant negative partial correlation between APF and improvement on HAMD_{17} (r(80) = -0.10, p = .38).

While patients with EEG abnormality reported more Anger-Hostility before treatment, there was no interaction with changes in Anger-Hostility during treatment and EEG abnormality (F(2, 112) = 1.87, \( \omega^2 = 0.01, p = .17 \)).

### 3.3. EEG abnormality and mood and cognition

Patients with and without EEG abnormality did not differ in either anxiety- or depression severity assessed by HAMD_{17} and the HAMD_{6} subscale (Table 2).

However, patients with an EEG abnormality had significantly higher total mood disturbance score (F(1, 87) = 4.38, \( \omega^2 = 0.04, p = .039 \), Fig. 1), on average 17.6 higher score on the POMS (CI: 0.9–34.2, Cohen’s \( d = 0.55 \)). The difference was mainly driven by Anger-Hostility (\( p = .017 \)). Patients with an EEG abnormality scored 5.7 (CI: 1.9–9.6, Cohen’s \( d = 0.78 \)) higher on the Anger-Hostility subscale than those without (F(1, 87) = 8.75, \( \omega^2 = 0.07, p = .004 \), Fig. 1).

Patients with EEG abnormality did not have poorer working memory assessed by LNS as evaluated. in an ANCOVA test adjusted for sex and age (F(1, 74) = 0.80, \( \omega^2 = 0.00, p = .38 \)). However, they had poorer verbal memory and remembered on average 2.6 (CI: 0.6–4.7, Cohen’s \( d = 0.76 \))
fewer words ($F(1, 79)=6.575, p=.012, \text{Fig. 1}$).

Since the patients with EEG abnormalities had poorer verbal memory and also reported more negative emotions in the form of anger and hostility, we, post-hoc, also examined differences in affective memory bias. The average affective memory bias in patients with EEG abnormalities was –5.8% indicating a trend that they recalled negative words (e.g., revenge and hate) better than positive words (e.g., joy and peace) compared to patients without EEG abnormalities whose mean affective bias was –0.9% (Cohen’s $d=0.48, p=.11$). However, when adjusted for age and sex, this group difference was not significant ($F(1, 79)=1.9, \omega^2=0.01, p=.17, \text{Fig. 1}$).

There was a positive linear relationship between poorer verbal memory and total mood disturbance adjusted for age, sex and EEG abnormality ($p=.031$, supplementary Figure S3) with no interaction with EEG abnormality.

### 3.4. EEG abnormality and treatment effects on verbal memory

While patients with EEG abnormality had poorer verbal memory before treatment, they had similar improvements in verbal memory over the 12 weeks of treatment ($F(1, 61)=0.31, \omega^2=0.00, p=.58$).

### 3.5. EEG abnormality after treatment

At week 8, follow-up EEG measurements were obtained from 38 patients. After 8 weeks of treatment, there were no new instances of EEG abnormalities, and one patient no longer exhibited pre-treatment EEG abnormalities. There was no statistically significant change in the prevalence of EEG abnormalities between pretreatment and follow-up ($p=1.00$).

### 4. Discussion

Previous research has highlighted abnormal EEG activity as a potential prognostic biomarker of non-response to specific SSRIs and SNRIs, such as escitalopram and venlafaxine, in MDD (Arns et al., 2015). We do not find that unmedicated patients with MDD with and without EEG abnormalities differ in depression severity. We also do not replicate that those with abnormal EEG activity have a poorer response to treatment including escitalopram at 8- and 12-weeks follow-up. Thus, our data do not support using EEG abnormalities as a predictive biomarker to guide antidepressant treatment selection.

Based on the iSPOT-D data, Vinne et al. reported that some patients who responded to another SSRI, sertraline, and had an abnormal EEG before treatment did not have an abnormal EEG at follow-up (based on only 2 min EEG recording) and suggested that this phenomenon could be attributed to a sertraline-specific mechanism involving the normalization of EEG patterns through the modulation of dopamine transporters. Initially, there were concerns about antidepressants having proconvulsive effects, based mainly on small case studies or individual patient reports (Kondziella and Asztely, 2009; Ware and Stewart, 1989). Although sertraline may indeed possess this capability, it is important to consider broader evidence from animal and clinical studies that suggest a general anticonvulsant effect of serotoninergic and noradrenergic antidepressants (Hong and Bainbridge, 2014; Jope and Browning, 2005; Kondziella and Asztely, 2009). This effect is thought to be mediated by the reduction of the potassium-evoked release of glutamate (Jope and Browning, 2005). Inconsistent with the iSPOT-D study findings (Arns et al., 2015), our research did not establish a association between EEG abnormalities and non-response to treatment options, including escitalopram (Arns et al., 2015). Taken together, it appears there may not be substantial evidence to suggest that sertraline performs more effectively in addressing EEG abnormalities among patients with depression when compared to other SSRIs or SNRIs.

The patients with EEG abnormality did have more severe mood disturbances and poorer verbal memory pretreatment. The abnormal EEG activity was predominantly bilaterally in frontotemporal regions, consistent with verbal memory issues; however, there were no detectable effects on their working memory.

There is evidence supporting that epileptiform discharges disrupt short-term cognitive processes in humans (Fernandez et al., 2015). However, collectively, there is currently limited and conflicting evidence that IEDs cause chronic cognitive deficits in humans (Fernandez et al., 2015; Meekes and Jennekens-Schinkel, 2018).

Although the patients with EEG abnormality had similar levels of depressive symptomatology, including anxiety prior to treatment, they did report worse mood and more anger and hostility. There are limited studies on EEG abnormalities and anger or aggression. Epileptiform discharges in healthy children aged 6–12 are not associated with emotional and behavioural problems (Okubo et al., 1994). In autism, IED is associated with more severe illness, behavioural problems, and social impairment (Veerappan et al., 2015).

Cognitive impairments can greatly affect the patient’s ability to function in everyday life and are often associated with high levels of subjective distress. Memory impairments have been associated with mood disturbances and anger (Lindert et al., 2021). This could explain why the patients with EEG abnormalities also reported greater mood disturbance, particularly feelings of anger.

EEG abnormality did not interact with improvement in mood or verbal memory during treatment, which suggests that the resting-state brain activity reflects an underlying brain pathophysiology or that it may take longer for the symptomatology and aberrant brain activity to normalise following treatment.

Although EEG abnormalities did not affect the results of medical treatment in this study, it is important to consider that having more severe verbal memory problems could have an impact on the effectiveness of psychotherapy. Previous research has shown that patients with post-traumatic stress disorder who have difficulties with verbal memory tend to have poorer outcomes with cognitive therapy (Wild and Gur, 2008).

Our findings should be interpreted in the light of several considerations.

The EEG data were rated by a blinded, single expert rater (O.U.C), as has been done elsewhere (Arns et al., 2015; Vinne et al., 2019). This approach may introduce bias; however, the inter-rater reliability of EEG abnormalities is generally high (Grant et al., 2014; Jing et al., 2020).

Our study found a 13.2% prevalence of IED and EEG slowing, slightly higher than the 9.4% reported in the study by Arns et al. (2015). This difference could be due to our three times longer EEG recording duration, which may have facilitated a more comprehensive evaluation and fewer false negatives. To further investigate the incidence of EEG abnormality in patients with MDD, future studies should ideally include longer recordings, e.g., a clinical EEG of ≥20 min, to limit false negatives. Provocation methods such as hyperventilation, intermittent photic stimulation, or sleep deprivation may also be used further to induce IEDs (Mendez and Brenner, 2006).

Additionally, it is worth noting that our study does not assess the association between EEG abnormalities and treatment response to sertraline and venlafaxine, as was done in the iSPOT-D dataset (Arns et al., 2015). The rarity of abnormal EEG activity and the limited sample size constrains the statistical power and the precision in estimating effect sizes. Future research could clarify the relationship between EEG abnormalities and antidepressant treatment response using large datasets such as the CAN-BIND-1 study (Zhdanov et al., 2020) and a current large-scale cohort study (Jensen et al., 2023).

### 5. Conclusion

In conclusion, we could not replicate previous findings of an association between pretreatment EEG abnormalities and non-response to escitalopram. This suggests that abnormal EEG may not be a reliable,
generalisable, and operable biomarker for predicting SSRI treatment outcomes and, therefore, not appropriate to use in routine clinical practice without further validation. Our study also reveals that abnormal EEG activity in the depressed state, pretreatment, is associated with mood disturbance and poor verbal memory. This emphasizes the potential of further research to advance the understanding of the relationship between EEG abnormalities, cognitive and affective deficits, and treatment outcomes to optimise treatment strategies and improve outcomes for patients with brain disorders.

**Declaration of competing interest**

CTI is a shareholder and has served as a consultant at DeepPhy AG. MBJ has given talks sponsored by H. Lundbeck and Boehringer Ingelheim. GMK has served as a consultant for SAGE Therapeutics and Sanos. VGF has served as a consultant for SAGE Therapeutics and Sanos.

**Funding**

documents/category/3-cimbi-database.

**Data availability**

The data analysed in this study is subject to the following licenses/restrictions: A Cimbi database application is required to access the study.

**Author contributions**


**References**


