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EEG measures of brain arousal in relation to symptom improvement in patients with major depressive disorder: Results from a randomized placebo-controlled clinical trial

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ABSTRACT

Hyperstable arousal regulation during a 15-min resting electroencephalogram (EEG) has been linked to a favorable response to antidepressants. The EMBARC study, a multicenter randomized placebo-controlled clinical trial, provides an opportunity to examine arousal stability as putative antidepressant response predictor in short EEG recordings. We tested the hypothesis that high arousal stability during a 2-min resting EEG at baseline is related to better outcome in the sertraline arm and explored the specificity of this effect. Outpatients with chronic/recurrent MDD were recruited from four university hospitals and randomized to treatment with sertraline ($n = 100$) or placebo ($n = 104$). The change in the Hamilton Rating Scale for Depression (HRSD-17) was the main outcome. Patients were stratified into high and low arousal stability groups. In mixed-model repeated measures (MMRM) analysis HRSD-17 change differed significantly between arousal groups, with high arousal stability being associated with a better outcome in the sertraline arm, and worse outcome in the placebo arm at week 4, with moderate effect sizes. When considering both treatment arms, a significant arousal group x time x treatment interaction emerged, highlighting specificity to the sertraline arm. Although findings indicate that arousal stability is likely to be a treatment-specific marker of response, further out-of-sample validation is warranted.

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1. Introduction

Antidepressant treatment in major depressive disorder (MDD) continues to be a challenge, as indicated by relatively low remission and high nonresponse rates (Murphy et al., 2021; Barlati et al., 2023), due to the lack of valid response predictors (Kennis et al., 2020). Reliable biological or clinical markers to robustly predict antidepressant treatment response in patients with MDD are still missing in both clinical care and research (Kennis et al., 2020). To address this issue, the multisite placebo-controlled randomized clinical trial—Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC)—systematically examined the value of multiple biomarkers (biosignatures) with combined predictive value of treatment outcome (Trivedi et al., 2016; Petkova et al., 2017).

Electroencephalogram (EEG)-derived neurophysiological measures provide direct information of different functional brain states and neuronal activation with high temporal resolution. Importantly, they are low cost measures with good test-retest reliability (Tenke et al., 2017, 2018). Within the EMBARC study there are two tiers of baseline patient characteristics, including clinical and biological parameters that have been pre-specified by the study team (Petkova et al., 2017). Pretreatment posterior alpha (Bruder et al., 2008; Tenke et al., 2011) and rostral anterior cingulate cortex theta activities are first tier predictors in the EEG data modality according to the EMBARC data analysis plan (Petkova et al., 2017), and pretreatment rostral anterior cingulate cortex theta activity has emerged as general prognostic marker for treatment outcome (Mulert et al., 2007; Pizzagalli et al., 2018). However, these two metrics differ in their validity and reliability which may negatively impact the clinical utility of frontal theta as a biomarker (Smith et al., 2020). EEG measures of arousal (Ulke et al., 2019a) are putative marker candidates of the third tier, which are defined as variables that were not pre-specified in the EMBARC data analysis plan, but that can be computed from the collected data. However, to avoid multicollinearity, these variables are subjected to independent screening and a selection process prior to combining them with other markers from a given modality (Petkova et al., 2017). In a first feasibility study, we examined the robustness of two correlated EEG measures (arousal stability and level) during a 2-min resting EEG, and found that arousal stability was more robust than arousal level (Ulke et al., 2019a). In the current study, we therefore examined the value of arousal stability for predicting clinical response to antidepressants.

In patients with depression, hyperstable brain arousal regulation has been consistently found during quiet rest (Hegerl et al., 2012; Schmidt et al., 2016; Ulke et al., 2017, 2019a) as indicated by high arousal stability. Given previous findings of upregulated arousal at baseline in antidepressant responders during a 15-min EEG at quiet rest (Schmidt et al., 2017), we tested the following hypothesis: Relative to MDD patients with low arousal stability during a 2-min resting EEG at baseline (as assessed by the VIGALL 2.1 algorithm (Hegerl et al., 2017)) MDD patients with high arousal stability will show a better response to sertraline at week 4. To explore the specificity of the effect, we performed the same analysis in the placebo arm, and examined the 3-way interaction between arousal group, visit week and treatment in secondary mixed-model repeated measures analysis.

2. Methods

2.1. Design, setting and study participants

In this multicenter randomized clinical trial outpatients with chronic or recurrent MDD without psychosis were enrolled between July 29, 2011, and December 15, 2015. Patients were recruited from four university hospitals, Columbia University Medical Center in New York (CU), Massachusetts General Hospital in Boston (MG), University of Texas Southwestern Medical Center in Dallas (TX) and University of Michigan in Ann Arbor (UM) (Tenke et al., 2017). Between testing sites, there was no significant difference in mean age or sex ratio. Over four weeks of treatment, the drop-out rate did not differ between the two randomizations groups for both the targeted EEG sample ($N = 204$; sertraline, 11/99, 11.1 %; placebo, 8/105, 7.6 %; $\chi^2[1] = 0.726$, $p = 0.39$) and the full sample ($N = 296$; sertraline, 19/146, 13.0 %; placebo, 15/150, 10.0 %; $\chi^2[1] = 0.661$, $p = 0.42$).

Main inclusion criteria were age between 18 and 65 (m/f), chronic (episode duration $>$ 2 years) or recurrent ($\geq$ 2 recurrences) non-psychotic MDD (according to DSM-IV) with an early onset (before age 30), fluency in English, and provision of written informed consent. Main exclusion criteria included diagnosis of bipolar disorder or schizophrenia (current or lifetime), other Axis I or II diagnoses (except for nicotine/caffeine dependence), or meeting DSM-IV criteria for substance abuse in the last 6 months (except for nicotine). The trial was conducted according to FDA guidelines and the Declaration of Helsinki. Signed informed consent was obtained from all participants at study entry.

2.2. Primary outcome measures

The change in the17-item Hamilton Rating Scale for Depression (HRSD-17; (Hamilton, 1960)) over four weeks (i.e., at baseline, and visit weeks 1, 2, 3, 4) served as outcome measure. Specifically, the change in the HRSD-17 total score (ΔHRSD-17) was assessed as percentage change at week 4 from baseline and calculated as follows: HRSD-17 baseline score minus estimated HRSD total score at week 4 divided by the HRSD-17 baseline score (x 100). The time frame was an a priori choice to optimize the time for clinical improvement with the number of drop-outs.

2.3. Data acquisition and processing

EEG data acquisition and processing harmonization has been previously described (Tenke et al., 2017); EEG labs of all four participating centers followed a standardized procedure, and on-site staff were certified by the Columbia lab to ensure satisfactory EEG data (Tenke et al., 2017; Ulke et al., 2019a). Briefly, continuous EEG data were recorded while participants sat quietly for four 2-minute periods in fixed order: eyes-open (block 1), eyes-closed (block 2), eyes closed (block 3), eyes-open (block 4). During the recording, participants were instructed to remain still, inhibit blinks or eye movements and, during the eyes-open condition, fixate a central cross on a monitor (Tenke et al., 2017). For the purpose of this study, only block 2 was examined (i.e., the first eyes-closed condition). Data were processed according to a standardized preprocessing pipeline as described by Tenke et al. (2017). Using VIGALL 2.1 (Hegerl et al., 2017) consecutive 1-s segments were classified into six different EEG-vigilance stages based on frequency bands and source localization with LORETA (Pascual-Marqui et al., 2011). Thereafter, each EEG vigilance stage was assigned a score, ranging from 6 to 1 ((Ulke et al., 2019a); Suppl. Table S1). The VIGALL software is licensed under GPL3 and available at https://github.com/danielboettger/VIGALL/.

2.4. EEG measures of arousal

To quantify arousal stability during the 2-min resting EEG at baseline we calculated an *arousal stability index* that was based on sliding 1-min intervals (interval 1: segments 1–60, interval 2: segments 2–61, interval 3: segments 3–62 etc.). A high score indicated a high arousal stability (Suppl. Table S2), scoring criteria are described in more details elsewhere (Ulke et al., 2019a). To obtain equal group sizes patients were stratified via median split into high and low arousal stability subgroups. The histogram of arousal stability indices based on treatment arm (sertraline vs placebo) is presented elsewhere (Suppl. Fig. S1).

2.5. Statistical analyses

In a first step using Chi-square tests, Mann-Whitney U tests and *t*-tests for independent sample comparisons, respectively (dependent on the scale of measurement for the dependent variables and their distribution), we investigated whether there were significant differences between arousal subgroups in the sertraline and the placebo arm regarding demographic and clinical variables in order to be able to identify relevant covariates. In a second step, we conducted mixed-model repeated measures (MMRM) analyses in both arms over 4 weeks of treatment, including fixed effects of covariates when indicated. We used MMRM to address the problem of dropouts and the differences between groups regarding this aspect (Twisk, 2013). The MMRM approach allows the utilization of all available and usable data; it is known to be flexible in modeling of time effects and advisable regarding the handling of missing data in an adequate way (Gueorguieva and Krystal, 2004). We applied the restricted maximum likelihood algorithm. The mixed model was built up step by step, adding independent variables, covariates and random effects to the model one after the other. At each step, the model's −2 log likelihood and the Bayesian Information Criterion (BIC) were considered—if it improved significantly compared to the previous step, the added parameter was retained (Suppl. Tables S3–S5). Significance was tested using the chi-square distribution (−2 log likelihood). The aim was to obtain a model that had both a high model quality (i.e. it contained all influential parameters) and no unnecessarily complex structure.

In the final MMRM analysis we included as fixed factors arousal group (high vs. low arousal stability), time (visit weeks 0, 1, 2, 3, 4) as well as covariates in the sertraline arm, and the interaction between arousal group and time. We treated intercepts as randomly varying across study participants. The statistical significance of the fixed effect of the interaction between arousal group and time was utilized to determine whether the change of HRSD-17 over time differed across arousal groups. To test our hypothesis (H1: *high* vs. *low arousal stability during a 2*-min *resting EEG at baseline is related to better outcome in the sertraline arm*) we computed ΔHRSD-17 values (baseline to week 4 change in percentages) in the sertraline arm, based on the predicted values of the MMRM, and compared them between arousal groups. To explore the specificity of the effect, we performed the same analysis in the placebo arm. In secondary analyses we explored whether the effects are moderated by treatment arm, by examining the 3-way interactions between arousal group (high vs. low arousal stability), time (visit weeks 0, 1, 2, 3, 4) and treatment (sertraline vs. placebo) in MMRM analysis. For all statistical tests, the significance level was set at $p = 0.05$. Statistical analyses were performed with SPSS software, version 25.0 (IBM Corp., Armonk, New York, USA).

3. Results

3.1. Participants

During enrollment, a total of 634 patients were screened, and 296 were randomized to receive sertraline hydrochloride (≤ 200 mg daily) or placebo. Of those, nine patients dropped out before the first medication/placebo dose, leaving 287 participants for analyses. Among the remaining 287 patients, 266 patients had EEG recordings and 204 had usable EEG data (sertraline arm: $n = 100$, placebo arm: $n = 104$) for EEG vigilance analyses. Of the 204 participants 128 were women (Table 1).

3.2. Main analyses

Of the 100 patients randomized to the sertraline arm, 49 were assigned to the high (arousal stability index = 6) and 51 to the low arousal group (arousal stability index ≤ 5). In the sertraline arm, the two subgroups did not significantly differ regarding sex distribution ($\chi^2 = 0.85$, $df = 1$; n.s.), years of education ($Z = -0.51$; n.s.) and degree of right-handedness (EHI) score ($Z = -0.01$; n.s.). However, frequencies of high vs. low arousal groups differed regarding collection site ($\chi^2 = 8.35$, $df = 3$; $p = 0.039$) and the subgroup with lower arousal stability tended to have higher age ($Z = -1.85$; $p = 0.064$). Therefore, fixed effects of site and age were included in multivariate statistical analyses in the sertraline arm. In the placebo arm, 49 of the 104 patients were assigned to the high (arousal stability index = 6) and 55 to the low arousal group (arousal stability index ≤ 5). The two subgroups did not significantly differ regarding age ($t_{102} = -0.52$; n.s.) sex distribution ($\chi^2 = 0.087$, $df = 1$; n.s.), years of education ($Z = -0.30$; n.s.), collection site ($\chi^2 = 5.59$, $df = 3$; $p = 0.133$) and EHI score ($Z = -0.04$; n.s.), and therefore no covariates were included in subsequent analyses.

In the sertraline arm, MMRM analysis revealed a significant main effect of time ($F_{4,\ 101} = 35.70$; $p < 0.001$), indicating a decrease in HRSD-17 score over the four weeks. Further, there was no main effect of arousal group ($F_{1,\ 88} = 0.00$; n.s.). A significant interaction between arousal group and time ($F_{4,\ 101} = 2.57$, $p = 0.021$ [one-sided test]) revealed that patients with higher (vs. lower) arousal stability indices showed a different change of depressive symptoms over time, indicating better outcome in patients with higher arousal stability at baseline. Based on the predicted values of the mixed models (Fig. 1A), we computed ΔHRSD-17 values (baseline-week4) and compared them between arousal groups. The two subgroups significantly differed regarding ΔHRSD-17 values, indicating a greater symptom reduction in the high arousal stability group, mean percentage (SD) high vs. low: 42.01% (7.2) and 36.02% (7.9); Mann-Whitney U test: $Z = -3.975$, $p < 0.001$ [one-sided test], $r = 0.398$, $\eta^2 = 0.158$ (moderate effect, Fig. 1C).

In the placebo arm, MMRM analysis revealed a significant main

Table 1
Characteristics of MDD patients included in analysis.

	All (*N* = 204)		**Sertraline** (*n* = 100; high arousal *n* = 49)				**Placebo** (*n* = 104; high arousal *n* = 49)			
			high arousal		low arousal		high arousal		low arousal	
	Mean/Prop.	SD	Mean/Prop.	SD	Mean/Prop.	SD	Mean/Prop.	SD	Mean/Prop.	SD
Age, yrs.	36.3	13.2	33.7	13.8	38.1	13.3	35.8	13.3	37.1	12.6
Sex, female	.63		.71		.63		.57		.60	
Edu., yrs.	15.1	2.4	14.8	2.2	15.1	2.3	15.2	2.5	15.4	2.5
EHI, sc.	73.2	46.3	76.5	36.9	64.2	59.7	72.1	49.5	79.5	35.6
Bl HRSD, sc.	18.6	4.4	18.3	4.0	18.6	5.1	18.0	3.9	19.4	4.6
Center										
CU	.33		.45		.20		.43		.25	
UM	.19		.18		.22		.14		.22	
TX	.30		.27		.35		.31		.27	
MG	.18		.10		.24		.12		.25	

Annotations: MDD = Major Depressive Disorder; Prop. = Proportion; SD = Standard deviation; yrs = years; sc. = score; Edu.= Education; Bl = Baseline; HRSD = Hamilton Rating Scale for Depression; EHI = Edinburgh Handedness Inventory score (laterality quotient; Oldfield, 1971); CU = Columbia University, New York; UM = University of Michigan, Ann Arbor; TX = University of Texas Southwestern, Medical Center Dallas; MG = Massachusetts General Hospital, Boston.

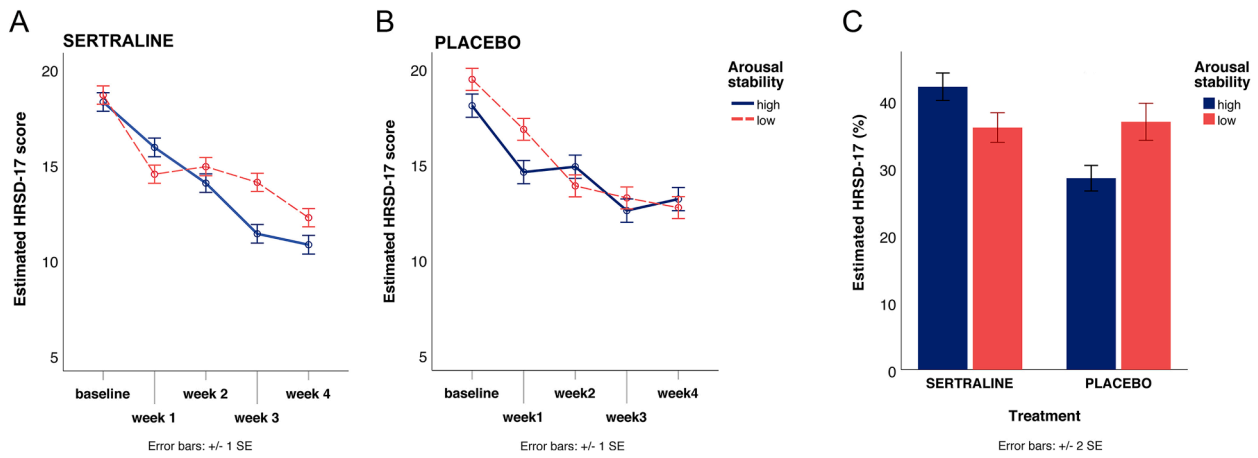

Fig. 1. Estimated Hamilton Rating Scale for Depression (HRSD-17) scores of high and low arousal stability groups in the (A) sertraline and (B) placebo arm based on the predicted values of the mixed-model repeated measures analyses. (C) Estimated ΔHRSD-17 values (baseline-week 4, in percentages) in high and low arousal stability groups in the placebo and sertraline arms. In the sertraline arm, patients with high arousal stability at baseline showed a more pronounced reduction of the HRSD-17 score as compared to patients with low arousal stability at baseline, while in the placebo arm, the effect went in the opposite direction.

effect of time ($F_{4,112} = 34.44$; $p < 0.001$), indicating a decrease in HRSD-17 score over the 4 weeks. There was no main effect of arousal group ($F_{1,93} = 0.34$; n.s.). A significant interaction between arousal group and time ($F_{4,112} = 3.34$, $p = 0.013$ [two-sided test]) revealed that patients with lower (vs. higher) arousal stability indices showed a different change of depressive symptoms over time. Contrary to the sertraline arm, the results indicated a better outcome in patients with lower arousal stability at baseline (Fig. 1C). Based on the predicted values of the mixed models (Fig. 1B), we computed ΔHRSD-17 values and compared them between arousal groups. The two subgroups differed significantly regarding ΔHRSD-17 values, but with reverse effects (mean percentage (SD) high vs. low: 28.5 % (6.7) and 36.9 % (10.2); Mann-Whitney U test: $Z = -4.868$, $p < 0.001$ [two-sided test], $r = 0.477$, $\eta^2 = 0.228$ (moderate effect, Fig. 1C).

3.3. Secondary analysis

Since arousal stability predicted response to sertraline in the sertraline arm over 4 weeks, we explored whether the effects were moderated by treatment arm. We therefore included a 3-way interaction of the factors treatment (sertraline vs. placebo), arousal group (high, $n = 98$, vs. low, $n = 106$) and time (visit weeks 0, 1, 2, 3, 4) in MMRM analysis. The two arousal groups did not significantly differ regarding sex (high vs. low arousal stability: 63 [64.3 %] and 65 [61.3 %] female), years of education (mean ± SD, 15.0 ± 2.4 and 15.2 ± 2.4), and EHI score (74.3 ± 43.5 and 72.1 ± 49.1) at baseline, but they differed concerning study site ($\chi^2 = 12.8$, $p = 0.005$). Further, the subgroup with lower arousal stability tended to be older (high vs. low arousal stability: 34.7 ± 13.5 and 37.8 ± 12.8 years; $Z = -1.72$; $p = 0.085$). Thus, we integrated fixed effects of site and age in multivariate statistical analyses. MMRM analysis revealed a significant main effect of time ($F_{4,218} = 68.28$; $p < 0.001$), but not of treatment ($F_{1,182} = 0.57$, $p = 0.452$) or arousal group ($F_{1,181} = 0.04$, $p = 0.851$). While there were no significant two-way interactions (time x treatment: $F_{4,218} = 0.89$; n.s.; arousal group x time: $F_{4,218} = 1.12$; $p = 0.349$; arousal x treatment: $F_{1,182} = 0.02$; n.s.), a significant interaction of arousal group x time x treatment ($F_{4,218} = 4.77$, $p = 0.001$ [two-sided test], small effect) was observed, confirming that symptom reductions were most pronounced for the higher arousal stability group receiving sertraline.

4. Discussion

EEG measures of brain arousal have been suggested as markers for antidepressant treatment response. In the context of the EMBARC study, a clinical trial with patients randomized to treatment with sertraline hydrochloride or placebo, we examined the value of arousal stability, as assessed with VIGALL 2.1 (Hegerl et al., 2017), for the prediction of treatment outcome. Our main hypothesis was confirmed: high arousal stability during a 2-min resting EEG at baseline predicted greater depression improvement after 4 weeks in the sertraline arm as assessed by changes in HRSD-17 sum score. Second, the effect was specific to the sertraline arm, whereas it was reversed in the placebo arm. Third, in secondary analysis, the interaction between treatment, arousal group and time was significant. Taken together, these findings indicate that arousal stability may be a candidate for a treatment-specific marker of symptom improvement, rather than a general prognostic predictor.

The present findings corroborated findings of an earlier study using VIGALL 2.1 to examine EEG measures as predictors of antidepressant response, where we reported a higher frequency of high EEG vigilance stages in antidepressant responders as compared to non-responders (Schmidt et al., 2017). However, those findings were based on 15-min resting EEG data stemming from a smaller sample ($N = 65$) and no single variable was computed indexing arousal stability (Schmidt et al., 2017). Conversely, another study found an association between the propensity towards lower EEG vigilance stages over time and the response to selective serotonin reuptake inhibitors (SSRI) treatment (Olbrich et al., 2016) which is contrary to our findings. We attribute this discrepancy to differences in parametrization, and to the application of a newer version of the VIGALL algorithm having improved classification accuracy and less susceptibility to eye artifacts (Hegerl et al., 2017). Still, given these conflicting findings, additional studies using an independent dataset with comparable processing, classification and parameterization procedures as employed in the current study are warranted.

Consistently, previous EEG studies examining arousal stability in MDD patients during resting-state conditions described hyperstable arousal regulation in MDD when compared to healthy controls (Hegerl et al., 2012; Olbrich et al., 2012; Schmidt et al., 2016; Sander et al., 2018; Ulke et al., 2019b, 2019a), and arousal stability has been associated with depression severity in SSRI-medicated patients (Ulke et al., 2019b). Posterior alpha wave activity has been associated with better response to antidepressant treatment (Bruder et al., 2008; Tenke et al., 2011), which is consistent with the current finding of better HRSD-17 response in the high arousal group with predominant occipital alpha activity. Animal studies have repeatedly shown that SSRIs decrease the neuronal firing rate of the locus coeruleus (LC) (Grant and Weiss, 2001; West et al., 2009) known to modulate brain arousal (Berridge and Waterhouse, 2003; Maness et al., 2022). The noradrenergic LC system balances cortical excitation and inhibition by thalamocortical alpha

synchronization (Dahl et al., 2022), thereby modulating cortical states (Weiss et al., 2024). Thus, we speculate that the depressive symptom reduction may be partially mediated by the noradrenergic LC system, as postulated by the arousal regulation model of affective disorder (Hegerl and Hensch, 2014).

There are several limitations to the current study. The analyses utilized a previously published dataset, and the examined parameter and outcome measures were not part of the original study analysis plan, although secondary analyses had been intended (Petkova et al., 2017) and we chose the outcome measures a priori. VIGALL analyses were performed in a dataset that had been processed using a different standard procedure concerning artifact correction than previous studies utilizing VIGALL. Moreover, VIGALL-based measures (based on 15–20 min EEG recordings) have been shown to have good validity (Jawinski et al., 2017; Huang et al., 2018) and reliability (Huang et al., 2015), but validation studies of VIGALL parameters based on shorter EEG-recordings are missing. However, in a feasibility study we were able to demonstrate the applicability of this algorithm in the EMBARC dataset (Ulke et al., 2019a). The 3-way interaction of arousal group, treatment and time is in part based on baseline HRSD-17 differences between high/low arousals group in the placebo arm. Although effect sizes concerning ΔHRSD-17 were moderate in either arm, their direction nonetheless supported the specificity of the effect. Finally, because the original study used relatively strict inclusion criteria, results may not easily generalize to other samples. Strengths include the study design, the harmonization of EEG data acquisition and processing across study centers and the sample size.

5. Conclusion

As hypothesized, higher arousal stability specifically predicted treatment response to sertraline but not to placebo. Replications in independent samples are warranted. Before considering arousal stability for inclusion in a composite index for personalized treatment decisions in the context of the EMBARC study, as described by Petkova et al. (2017), the predictive accuracy of this biomarker, alone and in combination with other biomarkers, should be tested in an adequately powered sample.

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CRediT authorship contribution statement

Christine Ulke: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Jürgen Kayser:** Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Craig E Tenke:** Supervision, Software, Project administration, Methodology, Data curation, Conceptualization. **Roland Mergl:** Methodology, Formal analysis, Validation, Writing – review & editing. **Christian Sander:** Methodology, Software, Validation, Writing – review & editing. **Lidia YX Panier:** Writing – review & editing. **Jorge E Alvarenga:** Data curation, Writing – review & editing. **Maurizio Fava:** Conceptualization, Funding acquisition, Writing – review & editing. **Patrick J McGrath:** Conceptualization, Funding acquisition, Writing – review & editing. **Patricia J Deldin:** Conceptualization, Funding acquisition, Writing – review & editing. **Melvin G McInnis:** Conceptualization, Funding acquisition, Writing – review & editing. **Madhukar H Trivedi:** Conceptualization, Funding acquisition, Writing – review & editing. **Myrna M Weissman:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Diego A Pizzagalli:** Conceptualization, Funding acquisition, Writing – review & editing. **Ulrich Hegerl:** Conceptualization, Methodology, Software, Supervision, Writing – review & editing. **Gerard E Bruder:** Conceptualization, Funding acquisition, Methodology, Validation, Supervision, Writing – review & editing.

Declaration of competing interest

In the last three years, the authors report the following financial disclosures, for activities unrelated to the current research:

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Supplementary materials

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