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Emotion-Induced Frontal Alpha Asymmetry as a Candidate Predictor of Relapse After Discontinuation of Antidepressant Medication

Isabel M. Berwian, Marius Tröndle, Carlota de Miquel, Anastasios Ziogas, Gabor Stefanics, Henrik Walter, Klaas E. Stephan, and Quentin J.M. Huys

ABSTRACT

BACKGROUND: One in 3 patients relapse after antidepressant discontinuation. Thus, the prevention of relapse after achieving remission is an important component in the long-term management of major depressive disorder. However, no clinical or other predictors are established. Frontal reactivity to sad mood as measured by functional magnetic resonance imaging has been reported to relate to relapse independently of antidepressant discontinuation and is an interesting candidate predictor.

METHODS: Patients (n = 56) who had remitted from a depressive episode while taking antidepressants underwent electroencephalography (EEG) recording during a sad mood induction procedure prior to gradually discontinuing their medication. Relapse was assessed over a 6-month follow-up period. Thirty five healthy control participants were also tested. Current source density of the EEG power in the alpha band (8–13 Hz) was extracted and alpha asymmetry was computed by comparing the power across 2 hemispheres at frontal electrodes (F5 and F6).

RESULTS: Sad mood induction was robust across all groups. Reactivity of alpha asymmetry to sad mood did not distinguish healthy control participants from patients with remitted major depressive disorder on medication. However, the 14 (25%) patients who relapsed during the follow-up period after discontinuing medication showed significantly reduced reactivity in alpha asymmetry compared with patients who remained well. This EEG signal provided predictive power (69% out-of-sample balanced accuracy and a positive predictive value of 0.75).

CONCLUSIONS: A simple EEG-based measure of emotional reactivity may have potential to contribute to clinical prediction models of antidepressant discontinuation. Given the very small sample size, this finding must be interpreted with caution and requires replication in a larger study.

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Depression is the leading cause of disability and among the most burdensome disorders worldwide (1). The reason for this is in no small part due to its chronicity. The time spent in depression rises linearly with age among affected individuals (2), effectively taking away a substantial part of an individual's life. The risk of an episode is initially strongly affected by stressful life events, but over time becomes a self-propelling force (3,4), with the risk of chronicity increasing with each episode (5). Therefore, the goal of depression treatment must not only be the resolution of a particular episode but also the long-term prevention of relapses.

The choice of whether to discontinue an antidepressant medication plays an important role in this context because relapses frequently follow discontinuation: Around one-third of those who discontinue antidepressant medication suffer a relapse within months of discontinuation (6–10). Unfortunately, clinically salient features have little value in predicting who will relapse after discontinuation (11,12). For example, estimates of the impact of the number of previous episodes diverge diametrically (6,8), while length of remission on medication does not relate to relapse risk (6–8,13,14).

Therefore, it may be useful and necessary to examine more affective, cognitive, or neurobiological measures as predictors of relapse risk after antidepressant discontinuation (15). Current mood and mood reactivity but not cognitive reactivity have been shown to be associated with relapse independent of antidepressant discontinuation (16–18). Consistent with Teasdale's differential activation hypothesis (19), sadness-induced maladaptive cognitions (20,21) and functional magnetic resonance imaging (fMRI) measures of induced sadness (22) or self-blame (23) have all been reported to predict relapse. Therefore, the induction of emotions associated with the depressed state appears to be a promising probe. Furthermore, Farb *et al.* (22) found that brooding was related to a sadness-induced fMRI measure and subsequent relapse. They also replicated and extended their neuroimaging results in a randomized controlled trial that showed that somatosensory deactivation was associated with subsequent relapse, while a reduction of left dorsolateral prefrontal cortex activity due to

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prophylactic treatment might protect from later relapse (24). The procedure used by Farb *et al.* (22,24) is particularly appealing from a clinical perspective because it involves simply presenting participants with sad and neutral movies during neuroimaging. However, the reliance on fMRI is a hindrance to clinical translation due to availability, costs, and contraindications to MRI.

In an attempt to maximize the potential for clinical applicability, we recorded brain activity with electroencephalography (EEG) during sad mood induction. An EEG marker that has been related to both depressive episodes and emotion induction is frontal alpha asymmetry (FAA). FAA power is defined as the contrast of alpha power over the frontal right versus frontal left electrodes. Throughout this paper, FAA will refer to the asymmetry in alpha power such that negative values indicate more left alpha power and positive values indicate more right alpha power. It is important to note that EEG activity measured with electrodes on the scalp can, in principle, arise from anywhere in the brain. Therefore, source localization is needed to identify the potential anatomical source. In general, alpha power (frequency range of 8–13 Hz) has been found to be inversely related to cortical activity as measured by positron emission tomography and fMRI recordings (25–27), such that more left FAA power is indicative of more right cortical activity (28). FAA power appears to be driven by frontal areas (29) similar to those predictive of relapse in fMRI measurements (22).

Interpretation of FAA is often based on the approach-withdrawal model suggesting that more left FAA power is related to withdrawal motivation, while more right FAA power is related to approach motivation. According to this model, an individual's FAA reflects their affective style across contexts (30,31) and may be a trait marker of current and past depression (32) [see Thibodeau *et al.* (33) for a review]. However, recent meta-analyses based on more coherent and rigorous inclusion and quality criteria have found no consistent evidence for FAA as a diagnostic marker (34). The relationship between FAA and depression may be moderated by covariates such as comorbid anxiety and sex (33–36). FAA in combination with covariates may also be a promising prognostic marker, because older women who subsequently responded to selective serotonin reuptake inhibitors showed more right FAA (37), and FAA was associated with the onset of first episodes (38).

The capability model (39) suggests that it is the FAA specifically during emotional challenges that may be the more reliable indicator of affective style and motivational differences because it assesses the abilities to respond to, or more specifically regulate, emotions. Stronger left shifts of FAA power during emotion induction differentiate better between participants with current depression, participants with remitted depression, and healthy participants than static rest FAA measures (40–42). Here, we further enhanced reliability by applying a current source density (CSD) transformation to the data (42). Similarly, there is evidence for a left laterization of FAA power during emotion induction in children at risk for depression (43) and individuals with dysphoria (44) [see (45) for a review].

The specific role of responses to mood induction in the context of antidepressant discontinuation as opposed to more general relapse prediction has not been addressed. In addition, relapse specifically after antidepressant discontinuation may involve both pharmacological and psychological mechanisms. The knowledge that a potentially effective medication is being withdrawn may have a nocebo effect, and this may impact realistic clinical settings (46).

Therefore, in this study, we examined whether neural responses to mood induction assessed with EEG have potential in predicting relapse after open-label, naturalistic antidepressant discontinuation. Patients with remitted major depressive disorder were followed up after discontinuing their antidepressant medication and after viewing sad and neutral movies while EEG was recorded.

Based on previous results and in an attempt to extend the results by Farb *et al.* to EEG (22), we aimed to examine the role and predictive power of sadness-induced FAA and rumination in relation to disease and medication state and relapse after antidepressant discontinuation. Notably, we have previously reported that clinical and demographic variables do not predict relapse in this sample (12), highlighting the importance of identifying other potentially predictive measurements.

METHODS AND MATERIALS

Participants

The AntIDepressiva Absetzstudie (AIDA) study (12) was a bicentric antidepressant discontinuation study with sites in Zurich, Switzerland, and Berlin, Germany. It recruited healthy control participants and patients with either severe or recurrent DSM-IV-TR major depressive disorder (47), who had remitted from a major depressive episode while taking antidepressant medication (i.e., they did not fulfill the criteria for a depressive episode at study entry and had a score of <7 on the Hamilton Depression Rating Scale) and who intended to discontinue their medication (see Supplemental Methods for full inclusion and exclusion criteria). Participation in the EEG recording was an additional voluntary component of the study at the Zurich site only. All participants gave written informed consent, received monetary compensation for their time, and indicated whether they were willing to participate in an additional EEG session, which lasted for approximately 3 hours. The study was approved by the Cantonal Ethics Commission Zurich (BASEC: PB_2016-0.01032; KEK-ZH: 2014-0355).

Study Design

After providing consent, participants underwent a baseline session to assess inclusion criteria by trained staff, acquire baseline self-report and demographic characteristics, and plan the study assessments and discontinuation [see Berwian *et al.* (12) for full details]. They then underwent the EEG session prior to gradually tapering their antidepressant medication over a period of up to 18 weeks and entering a 6-month follow-up. Participants were contacted by telephone at weeks 1, 2, 4, 6, 8, 12, 16, and 21 after the end of medication discontinuation to assess relapse and were encouraged to contact the study team in case of a worsening of their mental state. If the telephone assessment indicated a possible relapse, they were invited for an in-person structured clinical interview. Relapse was defined as fulfilling the criteria for a major depressive

episode according to DSM-IV-TR (47). A final assessment was conducted if relapse occurred or 6 months after completing discontinuation. Study team members were not involved in treatment decisions. These remained fully with the treating physician and the participants. All participants also underwent 2 main assessment sessions involving fMRI and behavioral and biological testing [see Berwian *et al.* (12,48,49)].

EEG Experiment

Participants were asked to abstain from alcohol and coffee for 24 hours prior to the EEG recordings. A 64-channel EasyCap (EASYCAP GmbH) adapted to head size was fitted, and Abralyt gel was applied. The reference electrode was placed on the nose tip. Additional channels were placed underneath the left eye for electrooculogram and on the back to acquire an electrocardiogram. We aimed for impedances <5 kΩ and accepted impedances <10 kΩ.

Prior to the experiment, participants rated one 45-second extract from each of 4 movies—The Champ, Terms of Endearment, Stepmom, and The Sixth Sense [Farb *et al.* (22)]—in terms of their subjective sadness on 7-point Likert scales. The 2 movies with the highest subjective sadness were then chosen as the sad movies, with each lasting approximately 3 minutes. Two neutral movies of 2 minutes and 15 seconds duration were also chosen as control stimuli. All movie clips were then divided into segments lasting approximately 45 seconds, i.e., the sad movies were divided into 4 and the neutral movies into three 45-second clips. During the experiment, participants were comfortably seated in a shielded room and monitored via video. They passively viewed the clips in a fixed order: neutral movie 1 (3 clips), sad movie 1 (4 clips), neutral movie 2 (3 clips), sad movie 2 (4 clips). After each 45-second clip, they rated their subjective sadness on the same 7-point Likert scale.

Self- and Observer-Rated Measurements

Inclusion and exclusion criteria and disease history and course were assessed with the German translations of the Structured Clinical Interview for DSM-IV I and II (50). Residual symptoms of depression were assessed with the Hamilton Depression Rating Scale (51) and the Inventory of Depressive Symptomatology (52) while residual anxiety was measured with the 7-item Generalized Anxiety Disorder Scale (53). Rumination (54,55) was also assessed. Finally, we assessed verbal intelligence with the Mehrfachwahl Wortschatz Test (56), working memory with the digit span backwards test from the Wechsler Adult Intelligence Scale (57), cognitive processing speed with the Trail Making Test A (58), and executive processing speed with the Trail Making Test B (58).

Analysis

Data analysis was performed using MATLAB version 9.4.0.813654 (The MathWorks, Inc.) (www.mathworks.com) with SPM 12 version 7219 (https://www.fil.ion.ucl.ac.uk/spm/), MARA version 1.2 (https://github.com/irenne/MARA) (59), EEGLab version 14.1.1b (https://sccn.ucsd.edu/eeglab/index.php), and CSD (60) (http://psychophysiology.cpmc.columbia.edu/Software/CSDtoolbox/) toolboxes. Data were bandpass filtered between 0.5 and 40 Hz and divided into 1-second epochs with 500 ms overlap. Artifacts were removed first by using independent component analysis and MARA60, and epochs were rejected by thresholding. As recommended (61), CSD was then estimated using the CSD toolbox (62). CSD is the Laplacian, i.e., the second spatial derivative, of the scalp surface voltage, and it is used to estimate the current projected toward the skull and hence gives rise to the observed scalp potentials. CSD minimizes the influence of volume conduction in the measured signal and therefore enhances the detection of distinct focal patterns in the distribution of alpha power over the scalp. Consistent with previous literature on FAA in major depressive disorder, the power in the alpha band was estimated as average power in 8 to 13 Hz, applying a fast Fourier transform to the CSD estimates. Finally, the data were transformed with a logarithm to the base of 10 and multiplied by 10.

A priori analyses focused on the contrast between electrodes F5 and F6 (29). FAA was defined as right minus left frontal activity (F6 − F5) of the log-transformed data. Emotion-induced FAA (eFAA) was defined as FAA while watching sad movies minus FAA while watching neutral movies. Thus, negative eFAA indicates stronger induction of left lateralization during the emotional challenge. Unless indicated otherwise, group comparisons were 2-sample 2-tailed t tests. If a Kolmogorov-Smirnov test indicated that the data were not normally distributed, then nonparametric tests were applied instead. Individual correlations between eFAA and self-reported sadness were performed by averaging the eFAA over each of the fourteen 45-second clips and performing a linear correlation with self-reported sadness after each of the clips. Logistic regressions were performed using the MATLAB function glmfit.m. We included residual symptoms to control for baseline severity and brooding due their relationship to sadness-induced blood oxygen level–dependent (BOLD) activity and relapse in the study by Farb *et al.* (22) as covariates. Because we had already established that all available standard clinical and demographic variables did not predict relapse in this study, we did not include them in the current analyses (12). To assess out-of-sample prediction, leave-one-out cross-validation was performed; i.e., we first estimated beta coefficients for a logistic regression model using all but 1 participant and then used these estimates and a fixed threshold of 0.5 to predict relapse for the left-out participant. The significance of the balanced accuracy was assessed using a binomial test comparing to 0.5. We only included residual symptoms, brooding, and eFAA in these analyses for the reasons outlined above. No critical hyperparameters were tuned, and therefore nested cross-validation was not required. Medication load was computed as $100 \times d/m/w$, with d being the dose in mg, m being the maximal allowed dose in mg in the Swiss compendium (http://www.compendium.ch), and w being the weight in kg.

RESULTS

Participants

A total of 123 patients and 66 healthy control participants were included, and 56 of the 85 patients and 35 of the 40 healthy control participants at the EEG site (Zurich) agreed to participate in the additional EEG study. Of the 56 patients, 48 (86%) reached a study end point (Figure 1), with 14 (29%) suffering a relapse. Patients and control participants did not differ on age,

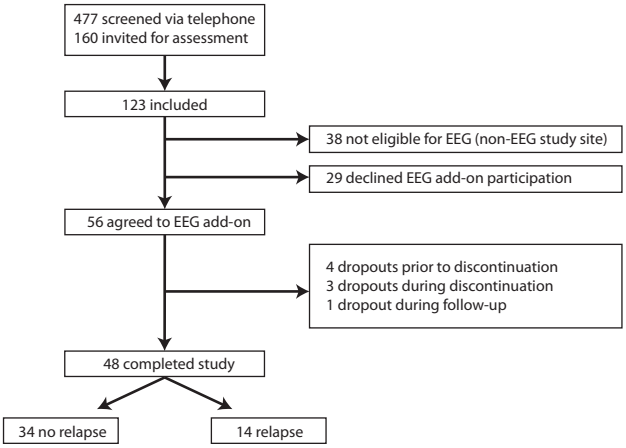

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. EEG, electroencephalography.

sex, body mass index, or neuropsychological variables (Table 1). Patients who went on to relapse and those who remained well after discontinuation did not differ in terms of number of prior episodes, onset age, medication load, or residual depression and anxiety symptoms or demographic and neuropsychological variables prior to antidepressant discontinuation (Table 1).

Sadness-Evoked Alpha Power

The sadness induction procedure proved to be effective. All groups showed a highly significant (all $ps < .0001$) but modest (around 1.5 points on a 7-point Likert scale) increase in sadness during the sad compared with the neutral movies (Figure 2A) that did not differ between any 2 groups (all $ps > .4$).

Nonparametric Wilcoxon tests were used as a Kolmogorov-Smirnov test indicated that eFAA and the correlation of eFAA and sadness were not normally distributed (all $ps < .001$). Note that *t* tests led to a similar pattern of results as reported below. Across all groups, we observed an eFAA, i.e., the sadness manipulation induced a shift in alpha power in CSD between electrodes F5/F6 ($Z = -3.5$, $p < .001$). The topography of the overall distribution of the effect (Figure 2B) indicated a broad shift in alpha power toward the left, but all statistical analyses focused on the electrode pair F5/F6 as prespecified. The shift was present at a trend level in control participants and more clearly in the patient group as a whole ($Z = -1.85$, $p = .06$ and $Z = -3.00$, $p = .003$, respectively) (Figure 3B). Patients and control participants did not differ overall ($Z = 0.49$, $p = .63$). However, among the patients, the effect was driven by those who would go on to remain well after antidepressant discontinuation ($Z = -4.01$, $p < .001$) (Figure 3C) and not present in those who went on to relapse ($p = .35$) (Figure 3C), which resulted in a significant difference ($Z = 2.82$, $p = .005$) with an effect size of Cohen's $d = 1.01$.

Furthermore, this shift in power was more pronounced the larger the self-reported sadness induced by the movies. This was true when examining all participants overall ($Z = -2.71$, $p = .007$) (Figure 3D) and among patients (right, $Z = -2.34$, $p = .02$) (Figure 3E) but not among control participants (left, $Z = -1.40$, $p = .16$) (Figure 3E), although the difference between patients and control participants was not significant ($Z = 0.40$, $p = .68$). Among patients, however, there was a

Table 1. Sample Characteristics

	Control Participants, $n = 35$	Patients, $n = 56$	p	Relapsers, $n = 14$	Nonrelapsers, $n = 34$	p
Sex, Female	25	44	.96	11	26	.99
Handedness, Left	0	2	.87	1	1	.98
Age, Years	32.97 ± 10.61	34.36 ± 11.01	.56	35.14 ± 9.11	33.12 ± 11.69	.57
BMI	22.92 ± 4.03	23.76 ± 4.15	.35	22.52 ± 3.17	23.81 ± 4.01	.29
HAMD-17[a]	0.55 ± 1.03	1.60 ± 1.66	.0019	1.38 ± 1.04	1.42 ± 1.64	.94
IDS-C[b]	0.71 ± 1.19	3.32 ± 2.81	4.4×10^{-6}	2.15 ± 1.28	3.30 ± 2.80	.16
GAD-7[c]	1.88 ± 1.98	2.80 ± 2.00	.038	2.71 ± 1.64	2.59 ± 2.08	.84
Onset Age, Years	–	23.77 ± 8.98	–	23.29 ± 6.78	23.24 ± 9.21	.99
Number of Prior Episodes	–	2.70 ± 1.31	–	2.64 ± 1.22	2.65 ± 1.32	.99
Medication Load	–	0.81 ± 0.42	–	0.70 ± 0.35	0.83 ± 0.45	.35
MWTB[d]	28.03 ± 4.36	28.05 ± 4.36	.98	29.21 ± 3.75	27.26 ± 4.83	.18
TMT A[e]	23.85 ± 5.91	24.16 ± 6.47	.82	21.49 ± 5.48	24.43 ± 6.82	.16
TMT B[e]	59.25 ± 22.47	59.12 ± 16.57	.98	53.79 ± 14.04	61.64 ± 18.31	.16
Digit Span[f]	8.00 ± 3.70	7.14 ± 2.18	.17	6.79 ± 1.67	7.03 ± 2.24	.72

Values are presented as mean ± 1 SD; *p* values show χ^2 for categorical and otherwise 2-sample *t* tests.

BMI, body mass index; GAD-7, 7-item Generalized Anxiety Disorder Scale; HAMD-17, Hamilton Depression Rating Scale, 17-item version; IDS-C, Inventory of Depressive Symptomatology, Clinician Rating; MWTB, Mehrfachwahl Wortschatz Test; TMT, Trail Making Test.

[a]See Williams (51).

[b]See Rush *et al*. (52).

[c]See Löwe *et al*. (75).

[d]See Lehr (56).

[e]See Reitan (58).

[f]See Wechsler (57) for digit span backwards from Wechsler Adult Intelligence Scale.

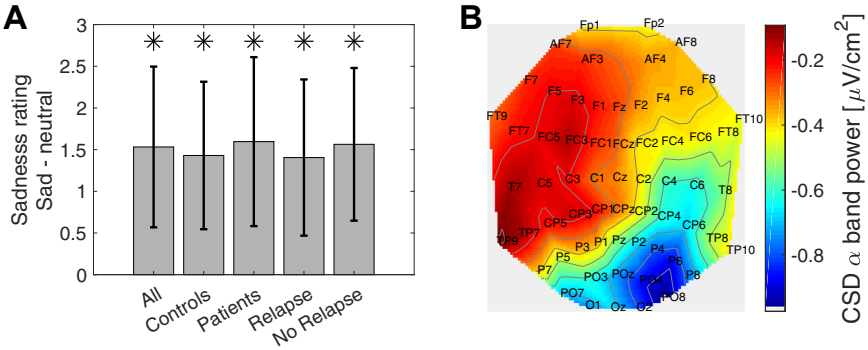

Figure 2. **(A)** Difference in sadness ratings between sad and neutral movies for all groups and subgroups. Error bars show ± 1 SD. *$p < .0001$ difference from 0. **(B)** Scalp plot of current source density (CSD) estimates in the alpha band comparing sad with neutral movie viewing showing an emotion-induced shift in alpha power toward the left across all participants in the study.

trend-level difference between those who did and did not go on to relapse ($Z = 1.86$, $p = .06$) (Figure 3F), with a correlation present among those who did not relapse ($Z = -2.09$, $p = .004$) but not among those who did relapse ($p = .64$).

Correlation With Rumination and Related Measures

As a consequence of the relapse/no relapse effect, emotion-induced alpha asymmetry was also correlated with depression severity at the study end point ($r = 0.39$, $p = .0056$) (Figure 4). The direction of this effect suggests that patients who showed an attenuated response in terms of left lateralization of FAA due to the emotion induction, i.e., consistent with emotional insensitivity, were more likely to have symptoms at the study end point. Notably, eFAA was not correlated with residual depression symptoms at baseline ($r = -0.038$, $p = .72$).

Farb *et al.* (22) reported that midfrontal sadness-induced BOLD reactivity was correlated with rumination scores and that this BOLD signal mediated the relationship between relapse and rumination. In the current sample, there was no correlation between sadness-induced alpha asymmetry and either total rumination scores or the brooding or reflection aspects of rumination.

Prediction

Next, we asked whether the EEG measure could improve relapse prediction above and beyond the residual depression symptoms and brooding. This logistic regression model achieved an area under the curve of 0.88 (Figure 5A) and a balanced accuracy with the optimally selected threshold of 0.86 (Figure 5B). Exclusion of eFAA resulted in a worse performance with an area under the curve of 0.72 (Figure 5A).

However, the above results do not represent true prediction because the parameters were fitted to the dataset that the model was then evaluated on. Furthermore, results of the regression analyses outlined above may be inflated due to small to moderate multicollinearity of residual depression symptoms and brooding ($r = 0.38$, $p = .008$). Next, we asked whether eFAA could improve out-of-sample prediction above and beyond residual symptoms and brooding. We estimated likely out-of-sample prediction through a leave-one-out cross-validation procedure. While residual depression symptoms and brooding did not predict relapse (balanced accuracy = 0.5, $p = .44$ and $p = .56$, respectively), eFFA predicted relapse with a balanced accuracy of 0.69 ($p = .007$), a positive predictive value of 0.75, a negative predictive value of 0.8, a sensitivity of 0.43, and a specificity of 0.94. Combining the 3 measures improved the balanced accuracy to 0.74 ($p = .0004$) (Figure 5C), with a positive predictive value of 0.73, a negative predictive value of 0.84, a sensitivity of 0.57, and a specificity of 0.91. Notably, we fixed the threshold applied in the current analyses a priori to 0.5 to avoid overfitting. Changing the threshold led to a different trade-off between sensitivity and specificity (Figure S1).

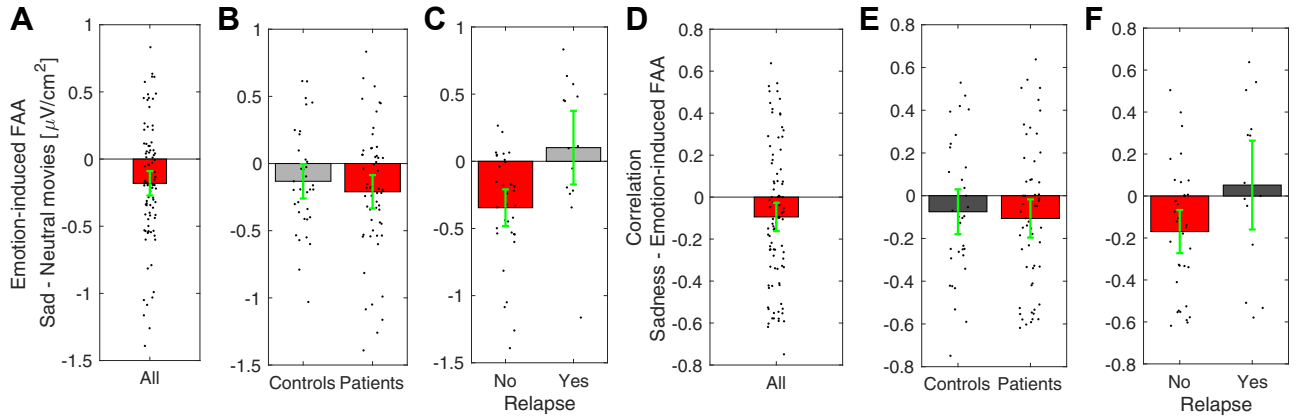

Figure 3. Alpha lateralization induced by sadness. Negative values indicate a lateralization to the left. **(A–C)** Shift in alpha power toward the left induced by sad movies compared with neutral movies. **(D–F)** Correlation of emotion-induced shift in alpha power with self-reported sadness induced by movies. Green error bars show 95% CIs. FAA, frontal alpha asymmetry.

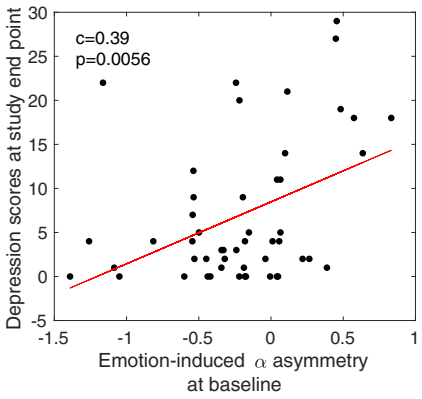

Figure 4. Emotion-induced alpha asymmetry correlated with Hamilton Depression Rating Scale scores at the study end point.

Exploratory Analyses

We confirmed our pattern of results with electrode pairs F4/F3, an electrode pair that has often been used in the literature (34) and alternative data transformations (see Supplemental Results). In contrast, we found no group differences in the neutral and sad conditions alone (see Figures S2 and S3).

DISCUSSION

Relapses after discontinuing antidepressant medications are common and occur in around one-third of cases within 6 months irrespective of the previous duration of medication (6–8). Our findings are very much in keeping with this. In the larger study, of which this is a subset, we have recently found that standard clinical variables have no predictive power (12). This highlights the need for other predictive markers, e.g., based on neurocognitive processes, to guide clinical decision making.

Here, we examined a relatively simple EEG measure that may have potential to be translated to clinical situations: watching emotional movie clips during EEG recording prior to initiating the medication discontinuation. The sad movies resulted in an eFAA, i.e., it induced a small but significant self-reported increase in sadness, and this was accompanied by a shift in frontal alpha current density from the right to the left, suggesting relative left hypoactivation of the frontal cortex. This effect differentiated patients who would go on to relapse from those who would remain well after discontinuing antidepressants, with no significant difference between the group of remitted patients as a whole and healthy never-depressed control participants.

Several points are worth noting. First, FAA induced by sad versus neutral movies was not able to distinguish between patients and control participants. Although some studies were able to differentiate between these 2 groups by using this marker [e.g., Stewart *et al.* (40); Grünewald *et al.* (62)], others failed to do so and recent meta-analyses failed to find a significant difference on FAA between participants with depression and healthy control participants (34,63). This conflicting evidence could be due to a variety of reasons. In their meta-analysis, Thibodeau *et al.* (33) concluded that several variables moderate the effect sizes of FAA as a marker for depression status. Larger effects were observed in adult samples with shorter EEG recording periods, with Cz references and midfrontal recording sites, and in younger childhood depression samples. Medication has also been previously found to reduce distinctions between patient and control groups (64), raising the possibility that the antidepressant medication normalizes frontal asymmetry. Of note, our entire patient sample was on antidepressant medication during the EEG assessment which could explain the lack of a group difference. In addition, our findings are consistent with evidence that FAA is related to the subsequent course of depression (37,38).

Second, the BOLD findings by Farb *et al.* (22,24) suggested that an increase in prefrontal reactivity to sad emotions and a lack of a reduction of this increase due to prophylactic treatment may index a higher relapse risk, respectively. Here, we observed a reduction in or no shift in FAA induced by the sad emotion in patients who went on to relapse. While this is neutral with respect to the overall activation, it suggests a reduction rather than an increase in neural reactivity to the emotional material. Furthermore, our finding indicates that

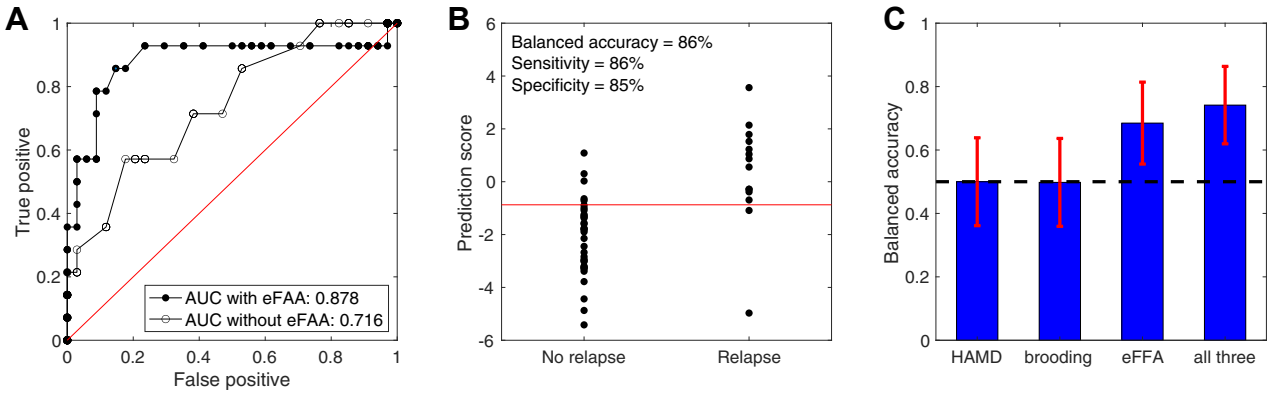

Figure 5. Relapse prediction. **(A)** The area under the curve increased from 0.72 without including emotion-induced frontal alpha asymmetry (eFAA) (empty circles) to 0.88 with eFAA included (black dots). **(B)** Optimal threshold showing classification on the weighted prediction score including eFAA. **(C)** Out-of-sample prediction. eFFA predicted relapse well above chance (0.69), while depression symptoms and brooding did not. The black dashed line indicates chance level. Error bars indicate 95% Bayesian credible intervals. AUC, area under the curve; HAMD, Hamilton Depression Rating Scale.

patients who relapsed were more similar to the control participants than to patients who showed a resilient course. This raises the possibility that individuals who have maintained neural markers of emotional reactivity while on antidepressants have had to acquire emotion regulation to maintain a euthymic mood, while individuals who have blunted emotional reactivity on antidepressants suffer a relapse because they have not acquired these mood regulation skills prior to discontinuing the medication. Our findings are consistent with reports that better immediate response to a cognitive restructuring intervention correlated with more alpha power in F3 versus F4 (65).

Depression is also often characterized by a blunted response to negative stimuli (66,67) and such a blunted response measured in terms of late positive potentials has been associated with worse outcome after cognitive behavioral therapy (68) and an increase in dysphoria (69). Blunted responses to negative stimuli might be a marker for a group of patients with a subtype of depression with worse prognosis. Hence, an alternative explanation for our pattern of results is that patients who are unresponsive to negative stimuli are more likely to relapse. Both explanations are in line with the result that less left lateralization in FAA during the emotional challenge was followed by more symptoms of depression at study end point.

Third, FAA has recently been related to left-lateral and dorsolateral prefrontal sources in depression (29) that appear more lateral than the medial prefrontal sources identified using BOLD (22). However, the replication by Farb *et al.* (24) in a larger randomized controlled trial indicated that a lack of attenuation of activity in the dorsolateral prefrontal cortex due to prophylactic cognitive therapy with a wellbeing focus or mindfulness-based cognitive therapy was related to subsequent relapse risk. Thus, the regions identified by Farb *et al.* (24) seem to overlap with the areas that generated FAA in the sample of Smith *et al.* (29). This pattern of results indicates that the regions driving the BOLD effects observed by Farb *et al.* (24) may be similar to those that drive the FAA effects in our sample.

Fourth, technical aspects of the associations and prediction results are worth reiterating. When fitting a model to the entire dataset, we found an association between residual symptoms and brooding and relapse even without eFAA but it was increased by eFAA. However, these analyses are not true prediction in the sense that they do not reflect prediction on unseen data. To approach this issue, we iteratively put the data of 1 participant aside, trained the model on all other data, and then asked how well the association generalized to the data not seen during training. This identified a predictive power with an out-of-sample balanced accuracy of 74% when eFFA was included, while residual symptoms and brooding alone each predicted relapse at chance level (50%). This suggests that 4 to 5 individuals need to be tested with EEG to predict outcome of one more patient correctly than when using simpler clinical procedures.

Fifth, patients who relapsed and patients who did not relapse did not differ in their self-reported sadness ratings of the movies, but they differed in their neural response assessed with EEG. In combination with our previous result that clinical and demographic data do not predict relapse after antidepressant discontinuation (12), this outcome indicates that more sophisticated procedures such as EEG may be helpful to identify patients who are likely to relapse after antidepressant discontinuation.

Our study has a number of strengths but also some limitations. A strength and limitation is the naturalistic design. Because discontinuation was open label, all of the current results could be driven either by pharmacological or psychological (nocebo) effects. Disentangling pharmacological and psychological effects of discontinuation requires a placebo-controlled study. While the inability to make causal statements is clearly a limitation, the naturalistic design also strengthens the clinical validity of the study because it captures relapse in a relevant setting where both pharmacological and psychological forces are jointly at play. Furthermore, while we used sadness as the target emotion, our study does not speak to whether this emotion is strictly necessary, and whether other emotions, or only aspects of emotions such as arousal, valence, or regulation strategy (70) are relevant.

However, the main limitation is the sample size, which is small. In particular, the relapse group consisted only of 14 patients. Thus, our result could also be a false-positive (i.e., a type I error). Nevertheless, we note the challenge in acquiring such samples. While quantitative EEG markers have long been thought to be promising, the literature suffers from heterogeneity, there is evidence for a substantial publication bias, and the sensitivity and specificity remain insufficient for clinical applications at present (71,72). Therefore, the current results (particularly in terms of prediction) should motivate additional studies but must be interpreted with great caution given the small sample size. Future studies with larger sample sizes will ideally combine this EEG marker with other potential predictors, regularization, and k-fold cross-validation to achieve a positive predictive value of 80%, which is considered to represent clinical usefulness (73). Such an approach has been shown to successfully predict relapse independent of antidepressant discontinuation (74). The sample is representative of the Swiss population and only includes White participants. The results may not generalize to members of other ethnicities.

Conclusions

We examined a simple EEG procedure in individuals who sought to discontinue their antidepressant medication after having achieved stable remission. The current findings provide preliminary evidence for this EEG marker as potential predictor of relapse, and if replicated, they may, in combination with technological advancement of developing portable and easy-to-use EEG electrodes, serve as the basis of a solution to support clinical decision making at the time of antidepressant discontinuation.

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QJMH and HW conceived and designed the study with input from KES. IMB, CdM, MT, GS, and AZ collected the data under the supervision of QJMH. KES was the study sponsor in Zurich. QJMH, KES, and HW acquired funding for the study. MT, IMB, AZ, GS, and QJMH planned and performed

the analyses. QJMH completed the analyses and wrote the manuscript. All authors provided critical comments and read and approved the final version of the manuscript. The funders had no role in the design, conduct or analysis of the study and had no influence over the decision to publish.

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Sharing data of this study conforms to the European Union regulations (GDPR) and Swiss data protection regulations. The decision will be based on the acceptance by the study team that a valid and timely scientific question, based on a written protocol, has been posed by those seeking to access the data. Safeguarding of ethical standards and legal obligations will be required. The role of the original study team will need to be acknowledged. Please contact the corresponding author via email to request access to the data. Data access for questions of scientific integrity may also be regulated via the funder. Access to code will be provided upon request.

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ARTICLE INFORMATION

From the Princeton Neuroscience Institute & Psychology Department, Princeton University, Princeton, New Jersey (IMB); Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich and ETH Zürich, Zurich, Switzerland (IMB, KES, QJMH); Methods of Plasticity Research, Department of Psychology, University of Zurich, Zurich, Switzerland (MT); Research Innovation and Teaching Unit, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain (CdM); Centro de Investigación Biomédica en Red de Salud Mental, Madrid, Spain (CdM); Faculty of Psychology, University Distance Suisse, Brig, Switzerland (AZ); Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary (GS); Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Psychiatry and Psychotherapy, Berlin, Germany (HW); Max Planck Institute for Metabolism Research, Cologne, Germany (KES); Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry, University of Zurich, Zurich, Switzerland (QJMH); Applied Computational Psychiatry Lab, Mental Health Neuroscience Department, Division of Psychiatry and Max Planck Centre for Computational Psychiatry and Ageing Research, Queen Square Institute of Neurology, University College London, London, United Kingdom (QJMH); and Camden and Islington NHS Foundation Trust, London, United Kingdom (QJMH).

Address correspondence to Isabel M. Berwian, Ph.D., at iberwian@princeton.edu.

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