Emotion-induced frontal α asymmetry as a candidate predictor of relapse after discontinuation of antidepressant medication

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Short title
EEG predictor of relapse after stopping antidepressant

ABSTRACT

Background: One in three 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 (MDD). However, no clinical or other predictors are established. Frontal reactivity to sad mood as measured by fMRI 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 EEG recording during a sad mood induction procedure prior to gradually discontinuing their medication. Relapse was assessed over a six-months follow-up period. 35 healthy controls were also tested. Current source density of the EEG power in the α band (8-13Hz) was extracted and alpha-asymmetry was computed by comparing the power across two hemispheres at frontal electrodes (F5 and F6).

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

Interpretation: 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.

1 INTRODUCTION

Depression is the leading cause of disability and amongst 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 amongst those affected (2), effectively taking away a substantial part of an individual's life. The riskof 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). Hence, 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 setting because relapses frequently follow discontinuation: around one third of those who discontinue antide-pressant medication suffer a relapse within months of discontinuation (6,7,8,9,10). Unfortunately, clinically salient features have little value in predicting who will relapse after discontinuation (11,12). For instance, estimates of the impact of the number of previous episodes diverge diametrically (6,8), while length ofremission on medication does not relate to relapse risk (6,7,8,13,14).

As such, it may be useful and necessary to examine more affective, cognitive or neurobiological mea-sures as predictors of relapse risk after antidepressant discontinuation (15). Current mood, as well as mood reactivity, but not cognitive reactivity have been shown to be associated with relapse independent of an-tidepressant discontinuation (16,17,18). In line 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. Hence, the induction of emotions associated with the depressed state appears to be a promising probe. Farb and colleagues (22) further found that brooding related to the sadness-induced fMRI measure and subsequent relapse. They further replicated and extended their neuroimaging results in a randomized controlled trial showing that somatosensory deactivation is associated with subsequent relapse, while a reduction of left dorso-lateral prefrontal cortex activity due to prophylactic treatment might protect from later relapse (24). The procedure by Farb *et al.* (22,24) is clinically particularly appealing as 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 maximise the potential for clinical applicability, we recorded brain activity with EEG during sad mood induction. An EEG marker that has been related to both depressive episodes and emotion induction is frontal α assymmetry (FAA). FAA power is defined as the contrast of alpha power over the frontal right vs frontal left electrodes. Throughout this paper, FAA will refer to the asymmetryin α power such that negative values indicate more left alpha power and positive values more right FAA power. Note that EEG activity measured with electrodes on the scalp can, in principle, arise from anywhere in the brain. Hence, source localisation is needed to identify the potential anatomical source.In general, α power (frequency range of 8 to 13 Hz) has been found to be inversely related to cortical activity as measured by PET and functional MRI recordings (25,26,27), such that more left FAA power isindicative 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 relates to withdrawal motivation, while more right FAA power relates to approach motivation. According to this model, an individual's FAA reflects their affective style across contexts (30,31) and mightbe a trait marker of current and past depression (32) (see Thibodeau *et al.* (33) for a review). Recent meta-analyses based on more coherent and rigorous inclusion and quality criteria, however, found no consistentevidence for FAA as a diagnostic marker (34). The relationship between FAA and depression might be moderated by covariates such as comorbid anxiety and gender (33,34,35,36). FAA in combination with covariates might also be a promising prognostic marker, as older women who subsequently responded to SSRIs 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 which mightbe the more reliable indicator of affective style and motivational differences as it assesses the abilitiesto respond to, or more specifically regulate, emotions. Indeed, stronger left shifts of FAA power

during emotion induction differentiate better between currently depressed, previously depressed, and healthy participants than static rest FAA measures (40,41,42). Here, we further enhanced the reliability by applying a current source density transformation to the data (42). Similarly, there is evidence for a left-lateralization of FAA power during emotion induction in children at risk for depression (43) and participants with dysphoria (44) (see (45) for a review).

The specific role of responses to mood induction in the setting 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 but also 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).

In this study, we therefore examined if 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 (MDD) 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 and colleagues 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. Of note, 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.

2 METHODS

2.1 PARTICIPANTS

The AIDA study (12) was a bicentric study with sites in Zurich, Switzerland and Berlin, Germany. It recruited healthy controls and patients with either severe or recurrent DSM-IV-TR Major Depressive Disorder (MDD) (47), who had remitted from a Major Depressive Episode while taking antidepressant medication (i.e. they did not fulfill the criteria of a depressive episode at study entry and had a score of less than 7 on the Hamilton Depression Rating Scale), and who were intending to discontinue their medication (see Supplementary Methods S1.1 full in- 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 approximately three hours. The study was approved by the Cantonal Ethics Commission Zurich (BASEC: PB_2016-0.01032; KEK-ZH: 2014-0355).

2.2 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 up to 18 weeks and entering a 6-months 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 the 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 additionally underwent two main assessment sessions involving fMRI, behavioural and biological testing (see Berwian *et al.* (12,48, 49)).
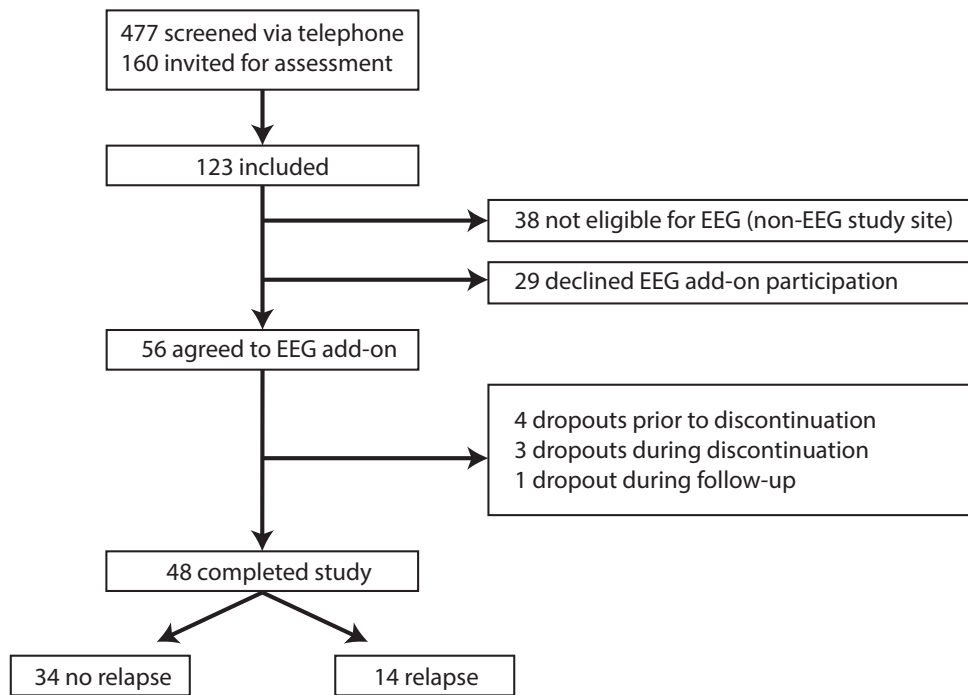
FIGURE 1: Consort diagram.

2.3 EEG EXPERIMENT

Prior to the EEG recordings, participants were asked to abstain from alcohol and coffee for 24h. A 64-channel EasyCap (EASYCAP GmbH, Herrsching, Germany) adapted to head-size was fitted and Abralyt gel 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 electrocardiogram. We aimed for impedances <5kΩ and accepted impedances <10kΩ.

Prior to the experiment, participants rated one 45s extract from each of four 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 two movies with the highest subjective sadness were then chosen as the sad movies, each lasting approximately 3 minutes. Two neutral movies of 2 min 15 second duration werealso chosen as control stimuli. All movie clips were then divided into segments lasting approximately 45 seconds, i.e. the sad movies were divided into four, and the neutral movies into three 45s 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) - neutralmovie 2 (3 clips) - sad movie 2 (4 clips). After each 45s clip, they rated their subjective sadness on the same 7-point Likert scale.

2.4 SELF- AND OBSERVER-RATED MEASUREMENTS

In- and exclusion criteria and disease history and course were assessed with the German translations of the Structured Clinical Interview for DSM-IV (SCID) 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 GAD-7 (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).

TABLE 1: Sample characteristics.

	Controls	Patients	*p*	Relapsers	Non-relapsers	*p*
N	35	56		14	34	
Gender (Women)	25	44	0.96	11	26	1
Handedness (left)	0	2	0.87	1	1	0.98
Age	32.97±10.61	34.36±11.01	0.56	35.14±9.11	33.12±11.69	0.57
BMI	22.92±4.03	23.76±4.15	0.35	22.52±3.17	23.81±4.01	0.29
HAM-D$_{17}$	0.55±1.03	1.60±1.66	**0.0019**	1.38±1.04	1.42±1.64	0.94
IDS-C	0.71±1.19	3.32±2.81	**4.4x10^{-6}**	2.15±1.28	3.30±2.80	0.16
GAD-7	1.88±1.98	2.80±2.00	**0.038**	2.71±1.64	2.59±2.08	0.84
Onset age	–	23.77±8.98	–	23.29±6.78	23.24±9.21	0.99
# prior episodes	–	2.70±1.31	–	2.64±1.22	2.65±1.32	0.99
Medication Load	–	0.81±0.42	–	0.70±0.35	0.83±0.45	0.35
MWTB	28.03±4.36	28.05±4.36	0.98	29.21±3.75	27.26±4.83	0.18
TMT A	23.85±5.91	24.16±6.47	0.82	21.49±5.48	24.43±6.82	0.16
TMT B	59.25±22.47	59.12±16.57	0.98	53.79±14.04	61.64±18.31	0.16
Digit Span	8.00±3.70	7.14±2.18	0.17	6.79±1.67	7.03±2.24	0.72

Shown are mean ±1 st. dev; p-values show χ2 for categorical and otherwise 2-sample t-tests. BMI = Body Mass Index; Digit span = digit span backwards from Wechsler Adult Intelligence Scale (57); GAD-7 = 7-item Generalized Anxiety Disorder Scale (59); HAM-D$_{17}$ = Hamilton Scale for Depression, 17-item version (51), MWTB = Mehrfachwahl Wortschatz Test (56); TMT = Trail Making Test (58);

2.5 ANALYSIS

Data analysis was performed using Matlab 9.4.0.813654 (www.mathworks.com) with SPM 12 v7219 (https://www.fil.ion.ucl.ac.uk/spm/), MARA v1.2 (https://github.com/irenne/MARA) (60), EEGLab 14.1.1b (https://sccn.ucsd.edu/eeglab/index.php) and CSD (61) (http://psychophysiology.cpmc.columbia.edu/Software/CSDtoolbox/) toolboxes. Data were bandpass filtered between 0.5 and 40 Hz and divided into 1s epochs with 500ms overlap. Artifact were removed first by using ICA and MARA60, and epochs rejected by thresholding. As recommended (62), Current Source Density was then estimated using the CSD toolbox (61). CSD is the Laplacian, i.e. the second spatial derivative, of the scalp surface voltage, and is used to estimate the current projected towards the skull and hence giving 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. In line with previous literature on FAA in MDD, the power in the α band was estimated as average power in 8-13 Hz applying a fast Fourier transform to the CSD estimates. Finally, the data was 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. eFAA was defined as FAA during while watching sad movies minus FAA while watching neutral movies. Thus, negative eFAA indicate stronger induction of left lateralization during the emotional challenge. Unless indicated otherwise, group comparisons were two-sample two-tailed t-tests. If a Kolmogorov-Smirnov indicated that the data was not normally distributed, non-parametric tests were applied instead. Individual correlations between eFAA and self-reported sadness were performed by averaging the eFAA over each of the 14 45s clips performing a linear correlation with the 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 its relation to sadness-induced BOLD activity and relapse in the study by Farb *et al.* (22) as covariates. As we had already established that all available standard clinical and demographic variablesdo not predict relapse in this study, we did not include them in the present 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 using all but one subject and then used these estimates and a fixed threshold
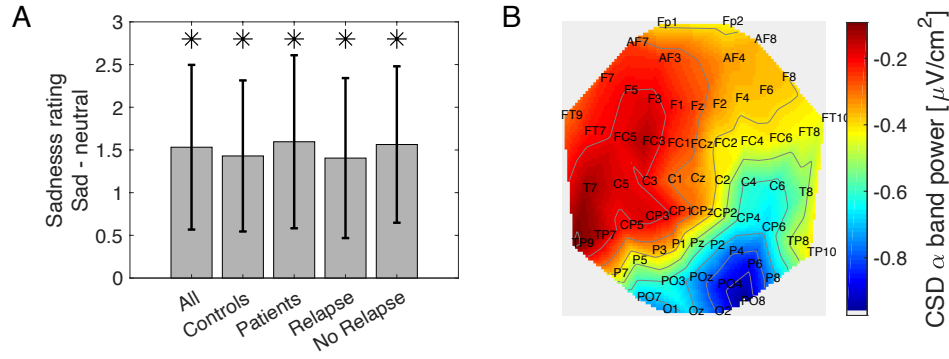
FIGURE 2: **A**: Difference in sadness ratings between sad and neutral movies for all groups and subgroups. Error bars show ±1 st. dev. * indicates p < .0001 difference from zero. **B**: Scalp plot of current source density (CSD) estimates in the α band comparing sad to neutral movie viewing, showing an emotion-induced shift in α power towards the left across all participants in the study.

of 0.5 to predict relapse for the left-out subject. The significance of the balanced accuracy was assessed using a binomial test comparing with 0.5. We only included residual symptoms, brooding and eFAA in these analyses due to the reasons outlined above. No critical hyperparameters were tuned and, thus, nested cross-validation was not required.

Medication load was computed as 100 x $d/m/w$, with d being the dose in mg, m being the maximal allowed dose in mg in the Swiss compendium (www.compendium.ch), and w being the weight.

3 RESULTS

3.1 PARTICIPANTS

123 patients and 66 healthy controls were included overall, and 56 of the 85 patients and 35 of the 40 healthy controls at the EEG site (Zurich) agreed to participate in the additional EEG study. Of the 56 patients, 48 (86%) reached a study endpoint (Fig. 1), with 14 (29%) suffering a relapse. Patients and controls did not differ on age, sex, BMI and neuropsychological variables (Tab. 1). Patients who would go on to relapse and those who would remain well after discontinuation did not differ in terms of numberof prior episodes, onset age, medication load, and residual depression and anxiety symptoms as well as demographic and neuropsychological variables prior to antidepressant discontinuation (Tab. 1).

3.2 SADNESS-EVOKED α POWER

The sadness induction procedure proved effective. All groups showed a highly significant (all p<0.0001) but modest (around 1.5 points on a 7-point Likert scale) increase in sadness during the sad compared to the neutral movies (Fig. 2A) that did not differ between any two groups (all p>.4).
Non-parametric Wilcoxon tests were used as a Kolmogorov-Smirnov test indicated that eFAA and the correlation of eFAA and sadness were not normally distributed (all p < 0.001). Note that t-tests led to a similar pattern of results as reported below. Across all groups, we observed an emotion-induced FAA (eFAA), i.e. the sadness manipulation induced a shift in α power in current source density between electrodes F5/F6 (Z=-3.5, p<0.001). The topography of the overall distribution of the effect (Fig. 2B) indicated a broad shift in α power towards the left, but all statistical analyses focus on the electrode pair F5/F6 as pre-specified. The shift was present at a trend level in controls and more clearly in the patient group as a whole (Z=-1.85, p=0.06 and Z=-3.00, p=0.003), respectively; Fig. 3B). Patients and controls did not differ overall (Z=0.49, p=0.63). However, amongst the patients, the effect was driven by those who would go on to remain well after antidepressant discontinuation (Fig. 3C; Z=-4.01, p<0.001)

and not present in those who went on to relapse (Fig. 3C; p=0.35), resulting in a significant difference (Z=2.82, p=0.005) with an effect size of Cohen's d'=1.01.
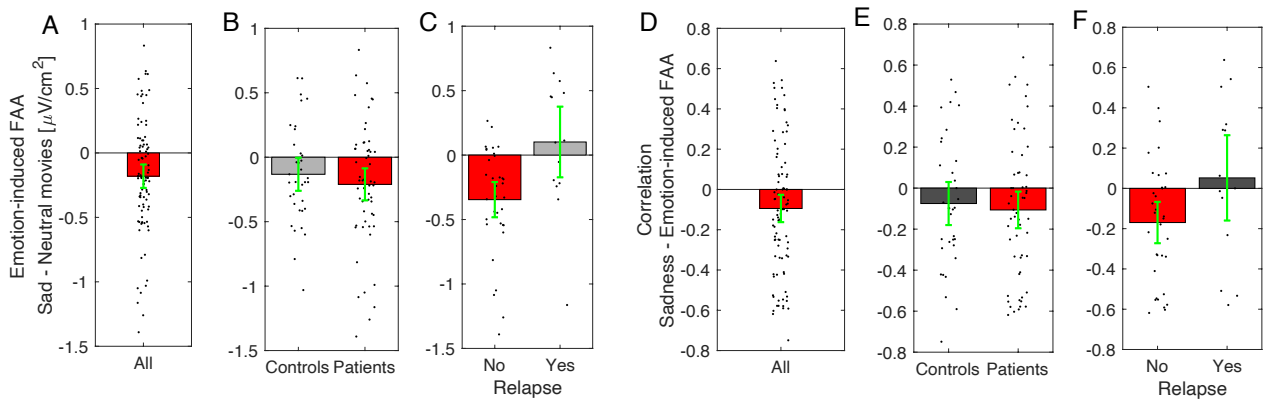

FIGURE 3: α lateralization induced by sadness. Negative values indicate a lateralization to the left. **A-C**: Shift in α power towards the left induced by sad movies compared to neutral movies. **D-F**: Correlation of emotion-induced shift in α power with self-reported sadness induced by movies. Green error bars show 95% confidence intervals.

Furthermore, this shift in power was more pronounced the larger the self-reported sadness induced by the movies. This was true when examining all subjects overall (Fig. 3D, Z=-2.71, p=0.007), and amongst patients (Fig. 3E, right, Z=-2.34, p=0.02) but not amongst controls (Fig. 3E, left, Z=-1.40, p=0.16), though the difference between patients and controls was not significant (Z=0.40, p=0.68). Amongst patients, on the other hand, there was a trend-level difference between those who did and did not goon to relapse (Z=1.86, p=0.06, Fig. 3F), with a correlation present amongst those who did not relapse (Z=-2.09, p=0.004) but not amongst those who went on to relapse (p=0.64).

3.3 CORRELATION WITH RUMINATION AND RELATED MEASURES

As a consequence of the relapse/no relapse effect, emotion-induced α asymmetry also correlated with the depression severity at study endpoint (Fig. 4, r=0.39, p=0.0049). 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. in line with emotional insensitivity, were more likely to have symptoms at study endpoint. Notably, eFAA did not correlate with residual depression symptoms at baseline (r=-0.038, p=0.72).

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

3.4 PREDICTION

Next, we asked whether the EEG measure could improve relapse prediction above and beyond the residual depression symptoms and brooding. This logistic regression achieved an area under the curve (AUC) of 0.88 (Fig. 5A), and a balanced accuracy with the optimally selected threshold of 0.86 (Fig. 5B). Exclusion of eFAA resulted in a worse performance with an AUC of 0.72 (Fig. 5A).
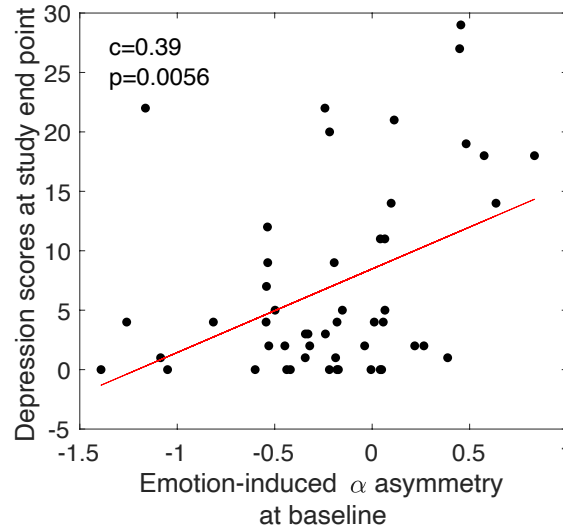
FIGURE 4: Emotion-induced α asymmetry correlated with the Hamilton score at study endpoint.

However, the above results do not represent true 'prediction' as the parameters are fitted to the dataset that the model is then evaluated on. Furthermore, results of the regression analyses above might be inflated due to small to moderate multicollinearity of residual depression symptoms and brooding (r=0.38, p=0.008). We next asked whether eFAA could improve out-of-sample prediction above and beyond the 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=0.44 and p=0.56, respectively), eFFA predicted relapse with balanced accuracy of 0.69 (p=0.007), with a positive predictive value (PPV) of 0.75, a negative predictive value (NPV) of 0.8, a sensitivity of 0.43 and a specificity of 0.94. Combining the three measures improved the balanced accuracy to 0.74 (p=0.0004; Fig. 5C) with PPV=0.73, NPV=0.84, a sensitivity of 0.57 and aspecificity of 0.91. Note, that we fixed the threshold applied in the present analyses a priori to 0.5 to avoid overfitting. Changing the threshold leads to different trade-off between sensitivity and specificity (supplementary Fig. S1).

3.5 EXPLORATORY ANALYSES

We confirmed our pattern of results with electrode pairs F4/F3, an electrode pair often used in the literature (34) and alternative data transformations (see supplementary results). In contrast, we found no group differences in the neutral and sad conditions alone (see Fig. S2 and Fig. S3).
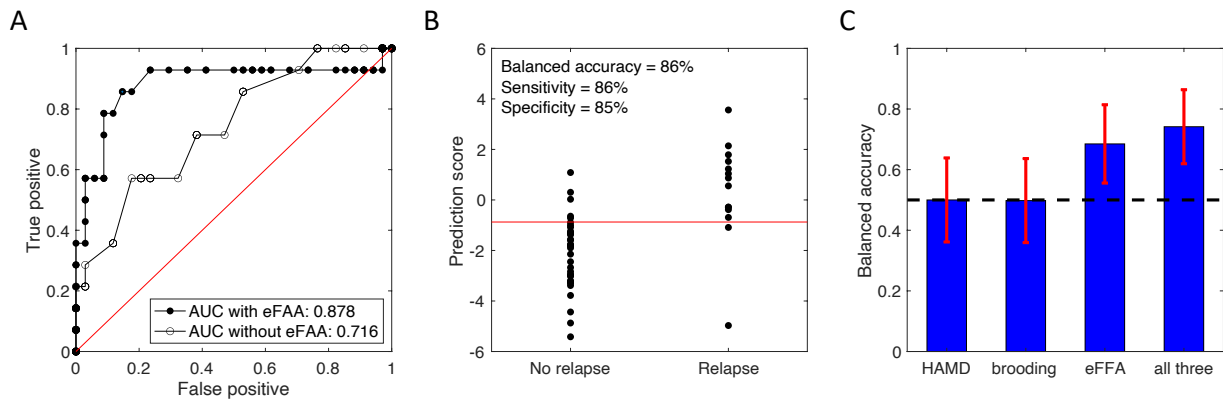
FIGURE 5: Relapse prediction. **A**: The area under the curve is increased from 0.72 without including eFAA (empty circles) to 0.88 with eFAA (black dots). **B**: Optimal threshold showing classification on the weighted prediction score including eFAA. **C**: Out-of-sample prediction. eFFA predicts relapse well above chance (0.69), while depression symptoms and brooding do not. The black dashed line indicates chance level. Error bars indicate 95% Bayesian credible intervals. eFFA = emotion-induced frontal α asymmetry; HAMD = Hamilton 17 rating scale for depression.

4   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 (6,7,8). 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 emotion-induced frontal α asymmetry (eFAA), i.e. it induced a small but significant self-reported increase in sadness, and this was accompanied by a shift in frontal α 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 remainwell after discontinuing antidepressants, with no significant difference between the group of remitted patients as a whole and healthy never-depressed controls.

Several points are worth noting. First, FAA induced by sad vs neutral movies was not able to distinguish between patients and controls. Although some studies were able to differentiate between these two groups by using this marker (e.g. Stewart *et al*. (40); Grünewald *et al.* (63)), others failed to do so and recent meta-analyses failed to find a significant difference on FAA between depressed participants and healthy controls (34,64). 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, withCz references and mid-frontal recording sites, and in younger childhood depression samples. Medication has also been previously found to reduce distinctions between patient and control groups (65), 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 in line with evidence that FAA relates to the subsequent course of depression (37,38).

Second, the BOLD findings by Farb *et al.* (22) and Farb *et al.* (24) suggested that an increase in prefrontal reactivity to sad emotions and a lack of a reduction of this increase due to prophylactic treatment might index a higher relapse risk, respectively. Here, we observe 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 does suggest a reduction in neural reactivity to the emotional material rather than an increase. Furthermore, our finding indicates that patients who relapse are more akin to the controls than those

who show a resilient course. This raises the possibility that those individuals who have maintained neural markers of emotional reactivity while on antidepressants have had to acquire emotion regulation to maintain an euthymic mood, while those who have a blunted emotion 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 vs F4 (66).

Depression is also often characterized by a blunted response to negative stimuli (67,68) and such a blunted response measured in terms of late positive potentials has been associated with worse outcome after Cognitive Behavioral Therapy (69) and an increase in dysphoria (70). 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 endpoint.

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 dorso-lateral prefrontal cortex due to prophylactic cognitive therapy with a well-being focus or mindfulness based cognitive therapy was related to subsequent relapse risk. Hence, the regions identified by Farb *et al.* (24) seem to overlap with the areas generating FAA in the sample by Smith *et al.* (29). This pattern of results indicates that the regions driving the BOLD effects 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 that 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 one subject 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 4-5 individuals need to be tested with EEG to predict outcome of one more patient correctly than when using simpler clinical procedures.

Fifth, relapsers and non-relapsers 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 might be helpful to identify those patients, who are likely to relapse after antidepressants discontinuation.

Our study has a number of strengths, but also 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 as it captures relapse in the relevant setting where both pharmacological and psychological forces are jointly at play. Furthermore, while we have 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 (71) are relevant.

The main limitation, however, is the sample size, which is small. In particular, the relapse group consists only of 14 patients. Thus, our result could also be a false positive.l. Nevertheless, we do 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 (72,73). The current results (particularly in terms of prediction) should hence motivate further studies, but must be interpreted with

great caution given the small sample size. Future studies with larger samplesizes ideally combine this EEG marker with other potential predictors, regularization and k-fold cross-validation to achieve a PPV 80% which is considered to have clinical usefulness (74). Such an approach has been shown to successfully predict relapse independent of antidepressant discontinuation (75). The sample is representative of the Swiss population and only includes white participants. The results might not generalize to members of other ethnicities.

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

DATA ACCESS

Sharing data of this study conforms to EU 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 additionally be regulated via the funder.

CODE ACCESS

Access to code will be provided upon request.

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4.2 CONFLICTS OF INTEREST

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4.3 CONTRIBUTIONS

QJMH and HW conceived and designed the study with input from KES. IMB, CM, 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, read and approved the manuscript.

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