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Amygdala Reactivity, Antidepressant Discontinuation, and Relapse

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IMPORTANCE Antidepressant discontinuation substantially increases the risk of a depression relapse, but the neurobiological mechanisms through which this happens are not known. Amygdala reactivity to negative information is a marker of negative affective processes in depression that is reduced by antidepressant medication, but it is unknown whether amygdala reactivity is sensitive to antidepressant discontinuation or whether any change is related to the risk of relapse after antidepressant discontinuation.

OBJECTIVE To investigate whether amygdala reactivity to negative facial emotions changes with antidepressant discontinuation and is associated with subsequent relapse.

DESIGN, SETTING, AND PARTICIPANTS The Antidepressiva Absetzstudie (AIDA) study was a longitudinal, observational study in which adult patients with remitted major depressive disorder (MDD) and currently taking antidepressants underwent 2 task-based functional magnetic resonance imaging (fMRI) measurements of amygdala reactivity. Patients were randomized to discontinuing antidepressants either before or after the second fMRI measurement. Relapse was monitored over a 6-month follow-up period. Study recruitment took place from June 2015 to January 2018. Data were collected between July 1, 2015, and January 31, 2019, and statistical analyses were conducted between June 2021 and December 2023. The study took place in a university setting in Zurich, Switzerland, and Berlin, Germany. Of 123 recruited patients, 83 were included in analyses. Of 66 recruited healthy control individuals matched for age, sex, and education, 53 were included in analyses.

EXPOSURE Discontinuation of antidepressant medication.

OUTCOMES Task-based fMRI measurement of amygdala reactivity and MDD relapse within 6 months after discontinuation.

RESULTS Among patients with MDD, the mean (SD) age was 35.42 (11.41) years, and 62 (75%) were women. Among control individuals, the mean (SD) age was 33.57 (10.70) years, and 37 (70%) were women. Amygdala reactivity of patients with remitted MDD and taking medication did not initially differ from that of control individuals ($t_{125.136}$ = 0.33; P = .74). An increase in amygdala reactivity after antidepressant discontinuation was associated with depression relapse (3-way interaction between group [12W (waited) vs 1W2 (discontinued)], time point [MA1 (first scan) vs MA2 (second scan)], and relapse: β, 18.9; 95% CI, 0.8-37.1; P = .04). Amygdala reactivity change was associated with shorter times to relapse (hazard ratio, 1.05; 95% CI, 1.01-1.09; P = .01) and predictive of relapse (leave-one-out cross-validation balanced accuracy, 67%; 95% posterior predictive interval, 53-80; P = .02).

CONCLUSIONS AND RELEVANCE An increase in amygdala reactivity was associated with risk of relapse after antidepressant discontinuation and may represent a functional neuroimaging marker that could inform clinical decisions around antidepressant discontinuation.

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Major depressive disorder is a major cause of disability globally, affecting more than 16% of adults during their lifetime. Much of its burden arises through its high rate of recurrence.[1] More than half of patients with a first episode of depression experience a second episode and the risk of relapse increases further with every additional experienced episode.[2] Therefore, prevention of relapse is important. Indeed, relapse risk in depression has been studied and some promising mechanisms have been identified,[3,4] although most risk factors associated with relapse are prognostic rather than prescriptive.[5]

One frequent and clinically relevant decision regarding the management of relapse risk is the decision whether to continue or discontinue antidepressant medication. Antidepressant medication discontinuation confers a substantial increase in relapse risk,[6,7] but antidepressant medications are often discontinued due to patient preference or other clinical reasons. Guidelines typically recommend 6 to 9 months of treatment after a first episode and longer after more episodes, although the evidence for these recommendations is equivocal[8-10] and based on assumptions about the natural course of depressive episodes.[11] In this situation, factors—particularly mechanistically interpretable ones—that can predict which patients may be at risk of relapse and may thus benefit the most from continued treatment would be helpful.

However, the mechanisms leading specifically to relapse after antidepressant medication discontinuation are not well understood.[12] Previous work has shown that the predictive power of demographic and clinical variables is limited.[12,13] Cognitive measures, such as behavioral assessments of effort sensitivity, have recently been found to be predictive of relapse after antidepressant medication discontinuation,[14] with evidence emerging also for electroencephalography and possibly resting-state functional magnetic resonance imaging (fMRI) measures.[15]

Neurobiologically, a highly promising process is amygdala reactivity to negative affective stimuli. Theories of depression and antidepressant medication treatment effect delays have considered it a marker of negative affective bias, which denotes the tendency to allow negative experiences to have a greater effect on one's psychological state than neutral or positive ones.[16-19] Negative affective bias, as measured by the amygdala activity in response to negative emotional faces, is thought to track the course of depression, being heightened in people in the acute depressive phase,[20-23] although it was not related to depressive symptoms in a large nonclinical older population-based sample,[24] indicating a more complicated relationship. Amygdala reactivity to negative stimuli is attenuated by tryptophan deletion, by both acute and repeated selective serotonin reuptake inhibitor administration in healthy individuals,[25-27] by emotion regulation interventions[28,29] relevant to the treatment of depression, and by antidepressant medication treatment.[20,30] There is meta-analytic evidence that amygdala reactivity to negative emotions reduces or normalizes with antidepressant medication treatment,[22,31-34] and studies suggest that pretreatment amygdala reactivity may be predictive of antidepressant medication treatment response.[31] Importantly, amygdala reactivity in the Hariri faces task has been extensively studied with evidence on its test-retest reliability[35] and inclusion in large-scale imaging datasets.[24]

Here, we examine whether amygdala reactivity is affected by antidepressant discontinuation and whether it has potential as a predictive biomarker for relapse. We report results from the Antidepressiva Absetzstudie (AIDA) study, a longitudinal, observational study where patients were tested before and shortly after antidepressant medication discontinuation and followed up for 6 months to assess relapse. We used a well-established fMRI paradigm that examines the blood oxygen level–dependent signal in the amygdala in response to facial emotion stimuli.[36] In keeping with the literature outlined above, we first expected that patients in remission before discontinuation would not differ from the control sample. Second, we expected that amygdala reactivity would increase with discontinuation, reflecting the converse of the established changes in response to antidepressant medication treatment.[31,33] Third, we expected that the increase in negative affective bias due to discontinuation would be related to the relapse risk. We conducted exploratory analyses to examine whether pretreatment amygdala reactivity or its change with discontinuation might have potential as predictors for relapse risk after discontinuation.

Key Points

Question Does antidepressant discontinuation increase amygdala reactivity to aversive stimuli, and is this increase associated with a risk of depression relapse?

Findings In this study, discontinuation of antidepressant medication increased amygdala response to negative facial expressions in individuals who eventually relapsed. The increase was associated with the risk of relapse.

Meaning The findings suggest that modulation of amygdala reactivity by antidepressant medications may represent a mechanism by which antidepressant medications help maintain remission and that how antidepressant discontinuation increases may affect relapse risk.

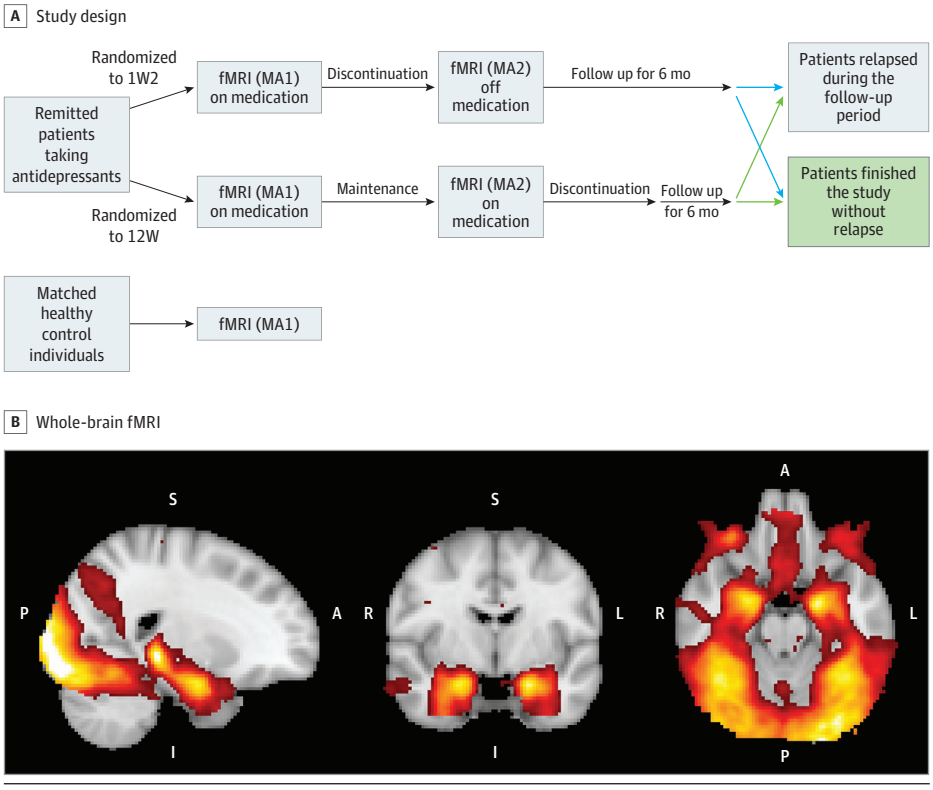
Methods

Ethical approval for this study was provided by the cantonal ethics committee in Zurich, Switzerland, and the ethics commission at the Campus Charité Mitte in Berlin, Germany. All procedures were in keeping with the Declaration of Helsinki. All participants provided written informed consent and received monetary compensation for participating.

Participants

The AIDA study recruited patients with remitted depression intent on discontinuing their antidepressant medication. Patients had experienced multiple or at least 1 severe[37] episode of major depressive disorder,[38] had initiated antidepressant treatment during the last episode, had reached a stable remitted state, and had reached the decision to discontinue

Figure 1. Study Design and Whole-Brain Functional Magnetic Resonance Imaging (fMRI) Results



A, Patients with remitted major depressive disorder were randomized to either undergo fMRI before and after antidepressant discontinuation or to undergo fMRI twice before antidepressant discontinuation. After discontinuation, all patients were followed up for 6 months. A group of control participants with no lifetime diagnosis of depression were assessed once only. The design enabled a cross-sectional comparison of the remitted depressed state (patients following a first scan [MA1] vs control individuals). In the patient sample, it allowed the effect of discontinuation to be compared to relapse (interaction of time point [MA1 vs second scan (MA2)] with group [discontinuation between the first and second scans (1W2) vs discontinuation after both scans (12W)] and relapse). B, Overall, the task significantly activated the amygdala across patients and control individuals. Shown is the *z* statistic map for the face-form contrast, with cluster-based correction with an activation threshold of $z > 3.1$ and a cluster-extent threshold of $P < .001$ applied at the whole-brain level.

their medication independently from and prior to study participation.

See eAppendix 1 in Supplement 1 for inclusion and exclusion criteria. Healthy control participants without a history of depression were matched for age, sex, and educational level. Participants were recruited in 2 university settings in Zurich, Switzerland, and Berlin, Germany.

Study Design

Figure 1 shows the study design. Participants were invited after a telephone screening and underwent an in-person assessment including clinical interviews with trained staff. Participants fulfilling all inclusion criteria were randomized into 1 of 2 discontinuation groups. Participants in the 1W2 group (discontinuation between the first and second scans) discontinued their antidepressant medication gradually (aiming for a discontinuation within 12 weeks but allowing up to 18 weeks) between assessments 1 and 2, allowing to control for repeated measurements of amygdala reactivity. Participants in the 12W group (discontinuation after both scans) underwent both assessments first, and then discontinued after the second assessment. At each of the assessment time points, participants completed a range of behavioral tasks, fMRI, and electroencephalography and had blood samples taken.[13-15] Relapse status was assessed during a 6-month follow-up period. At weeks 1, 2, 4, 6, 8, 12, 16, and 21 of the follow-up period, patients were contacted for telephone assessments to determine relapse status. In case relapse was deemed probable during the telephone assessment, patients were invited to an in-person clinical interview, and, if they fulfilled diagnostic criteria,[2] they underwent a final assessment. If no relapse occurred until week 26, they underwent the final assessment then. Control participants were only assessed once. Study data were collected between July 1, 2015, and January 31, 2019. Recruitment took place from June 2015 to January 2018. Statistical analyses were conducted between June 2021 and December 2023.

Faces Task

Participants performed the Hariri faces task[36] while undergoing fMRI scanning. In the task, individuals are asked to match the face depicted at the top of the screen to 1 of 2 faces at the bottom of the screen (one of these matches the top identically); all 3 faces either show angry or fearful emotions. In control trials, individuals select which of the geometric shapes at the bottom is identical to the target shape at the top. The task consisted of 8 alternating blocks of face and form trials, with 6 trials per block.

Statistical Analysis

The samples from Berlin and Zurich were analyzed together as 1 group. Throughout all regression analyses, site was included as a covariate of no interest. Group comparisons of symptom measures for patients vs control individuals and individuals who relapsed vs those who did not were performed via *t* tests. A post hoc test for an increase of amygdala reactivity in individuals who relapsed and who discontinued before the second assessment was performed via a paired-sample *t* test.

Table 1. Table With Sample Characteristics and *P* Values for Tests of Group Differences

Variable	Mean (SD)		*P* value	Mean (SD)		*P* value
	Control individuals (n = 53)	Patients (n = 83)		Did not relapse (n = 57)	Relapsed (n = 26)	
Demographic characteristics						
Age, y	33.57 (10.70)	35.42 (11.41)	.34	34.53 (11.57)	37.38 (11.02)	.29
Sex, No. (%)						
Female	37 (69.8)	62 (74.7)	.53	43 (75.4)	19 (73.1)	.82
Male	16 (30.2)	21 (25.3)		14 (24.6)	7 (26.9)	
BMI	23.49 (3.69)	23.99 (4.30)	.48	24.17 (4.31)	23.60 (4.34)	.58
Clinical measures						
Residual depression (IDS-C[40])	0.65 (1.07)	3.76 (3.96)	<.001	3.42 (2.91)	4.57 (5.71)	.25
No. of prior episodes	NA	2.41 (1.31)	NA	2.33 (1.34)	2.58 (1.24)	.43
Medication load[a]	NA	0.76 (0.40)	NA	0.78 (0.40)	0.72 (0.42)	.56
Neuropsychological scores						
Intelligence (MWTB[41])	28.08 (4.07)	28.60 (4.23)	.47	28.18 (4.30)	29.54 (3.98)	.17
Working memory (Digit Span Backward task of the WAIS[42])	8.17 (3.38)	6.93 (2.00)	.02	7.07 (2.16)	6.62 (1.58)	.34
Executive function (TMT A)[43]	23.3 (5.71)	24.82 (8.30)	.21	24.78 (8.20)	24.90 (8.68)	.95
Executive function (TMT B)[43]	56.52 (19.86)	56.55 (17.07)	.99	55.62 (17.03)	58.58 (17.32)	.45

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IDS-C, Inventory of Depressive Symptomatology, Clinician-Rated; MWTB, Mehrfachwahl-Wortschatz-Intelligenztest; NA, not applicable; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale.

[a] Defined as the dose divided by the maximal allowed dose according to the Swiss Compendium and by the weight of the participant.

fMRI Data Preprocessing

Detailed information regarding imaging data acquisition is provided in the eMethods in Supplement 1. Imaging data were preprocessed using standard settings of the FSL version 6.0 (FMRIB Software Library) FEAT software, with all steps described in the eMethods in Supplement 1. We checked for excessive motion by visual inspection of the output of the motion correction program MCFLIRT but did not exclude any participant as none showed a displacement greater than half the voxel size. General linear models were fitted to prewhitened data. The individual-level (first-level) general linear model design matrix included two 5000-millisecond boxcar regressors coding for the presentation of face and form stimuli, a stick function regressor for the button-presses, and 6 motion regressors obtained from the motion correction step during preprocessing. Regressors were convolved with a hemodynamic response function (mean [SD] lag, 6 [3] seconds). Each first-level general linear model included 3 contrasts: face, form, and face minus form. A group-level general linear model was performed using FEAT's FLAME method to obtain whole-brain estimates for the face vs form contrast.

Linear Mixed Effects Region of Interest (ROI) Analysis

Participant-wise first-level analyses were run using FEAT and resulting contrast estimates were transformed to MNI152 standard space for use in further analyses. Bilateral, left, and right amygdala ROIs were taken from the Harvard-Oxford subcortical atlas and used to extract the average estimates for each contrast (face, form, and face vs form). To assess the difference in amygdala response between patients in remission and healthy control individuals, we calculated a *t* test. We fitted a linear mixed model for the amygdala activity of only the patient group, for which we had measurements at 2 time points. We included time, discontinuation group (whether participants discontinued between the first scan [MA1] and the second scan [MA2] or discontinued after MA2), relapse status, age, sex, and site as predictors and participant-specific random intercepts. All models reported here converged. When reporting for left and right ROIs separately, the results are Bonferroni corrected.

Time to Relapse Analyses

To examine the association between amygdala reactivity and the relapse-free interval, we entered the difference in amygdala activity (ie, the per-person ROI-averaged contrast estimates) from MA1 to MA2 as a regressor into a proportional hazards Cox model with the time to relapse as the right-censored dependent variable and age and sex as additional regressors.

Prediction Analyses

The above analyses examined the association between the average of all voxels in the selected ROIs and the intervention or clinical outcomes. To examine whether amygdala reactivity might contain predictive information, we took a machine learning approach. The features included in the models consisted of the voxelwise face vs form contrast estimates returned from the first-level analysis of the patient sample. We included the estimates of all voxels of the amygdala ROI (based on the Harvard-Oxford subcortical atlas; 366 voxels for right amygdala, 306 for left, and 672 for bilateral). These were used as predictors in a logistic regression model to predict relapse status. We used L1 regularization (ie, variable selection) given the large number of features. Predictive performance was determined via leave-one-out cross-validation, with an inner (2-fold) cross-validation to find the optimal regularization parameter using gridsearch. We computed the posterior distribution of the balanced accuracy[39] to obtain estimates of the standard error and assess significance. We used 3 different

models. The first model used the amygdala activity during the first scan. The second model used only the amygdala activity from the second scan, and the third model used the difference (patientwise) of amygdala activity in each voxel of the amygdala mask. We corrected for multiple comparisons via Bonferroni-correction, with a corrected significance threshold of 1/160.

Analysis Plan

An analysis plan was created before data analysis commenced and is reproduced in the eAppendix 2 in Supplement 1. We deviated from the analysis plan in that standard amygdala ROIs based on the Harvard-Oxford subcortical atlas were used rather than individual ROIs. This was done to allow for a simpler analysis pipeline entirely within FSL with fewer degrees of freedom. We added separate analyses of left vs right amygdala ROIs and the predictive analyses.

Results

Of the 84 patients and 57 healthy control individuals who completed the study, 83 (mean [SD] age, 35.42 [11.41] years; 62 [74.7%] women and 21 [25.3%] men) and 53 (mean [SD] age, 33.57 [10.70] years; 37 [69.8%] women and 16 [30.2%] men), respectively, could be included in the analyses (eFigure 1 in Supplement 1). **Table 1**[40-43] shows the characteristics of the sample. The patient group was in remission, with minimal residual symptoms that were nevertheless higher than those in the control group and with some residual working memory impairments. At baseline, patients who went on to relapse and those who did not did not differ in any clinical or neuropsychological variable or in terms of medication.[13,44] The fMRI task was effective, resulting in an overall activation pattern like that reported in the literature, with prominent bilateral amygdala activation (Figure 1). The analyses reported here were limited to the amygdala ROI (**Figure 2**). In the following, we will denote ROI-averaged face-vs-form contrast estimates as amygdala reactivity.

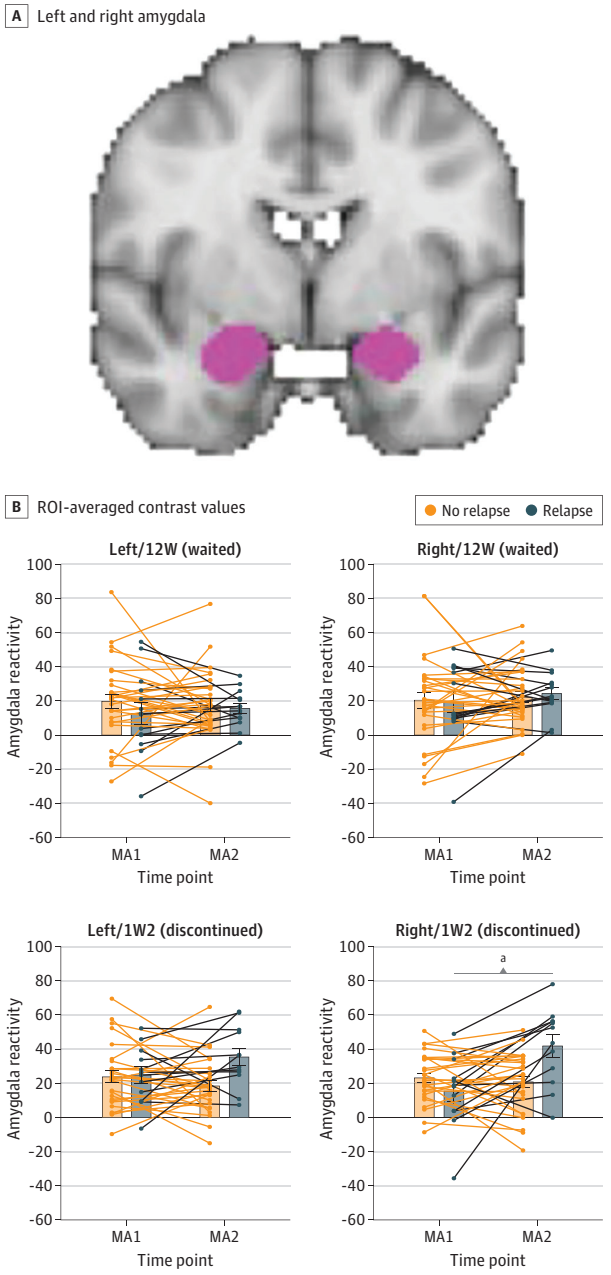
Patients in Remission vs Healthy Control Individuals

We compared amygdala reactivity in patients vs control individuals at assessment point 1. The bilateral ROI-averaged contrast estimates of both patient and control groups were significantly greater than zero (control group: n = 55; t_{52} = 8.32; P < .001; patients at first scan: n = 83; t_{82} = 9.54; P < .001), but did not differ between groups (t_{125} = 0.33; P = .74).

Association Between Amygdala Reactivity, Discontinuation, and Relapse

The results of the linear mixed model for the amygdala reactivity are depicted in **Table 2**. This model revealed that discontinuing antidepressant medication had a different effect for those who later did and did not relapse, as indicated by a significant 3-way interaction between time (MA1 vs MA2), discontinuation group (continuation vs discontinuation), and relapse status (relapse vs no relapse) at follow-up (β, 18.9; 95% CI, 0.8-37.1; P = .04) and as depicted in Figure 2. There were no main effects of group (z, 0.81; P = .42), time (z, −0.02; P = .98), or relapse (z, −0.49; P = .63). A post hoc paired t test indicated that this was driven by an increase in amygdala reactivity in patients who discontinued before the second assessment and who later went on to relapse (point estimate, 19.4; n = 12; t_{11} = 3.03; P = .01). At the second assessment, amygdala reactivity in the discontinuation group was higher for pa-

Figure 2. Region of Interest (ROI) Results



Panel (A) shows the 2 selected ROIs corresponding to left and right amygdala from the Harvard-Oxford atlas. Panel (B) shows the same ROI-averaged contrast values for patients for both time points and split by discontinuation group and relapse. Bars indicate means with standard errors.

[a]Indicates post hoc paired-sample t test P < .01.

Table 2. Coefficients of Mixed Model for the Bilateral Amygdala Response (ROI-Averaged Voxelwise Estimates of the Face vs Form Contrast)

Name[a]	β	SE	95% CI	*z* Value	*P* value
Intercept	16.62	4.38	8.03 to 25.21	3.79	<.001
MA2	−0.09	3.56	−7.06 to 6.88	−0.02	.98
1W2 group	4.16	5.15	−5.93 to 14.26	0.81	.42
Relapse	−3.05	6.25	−15.30 to 9.21	−0.49	.63
Site: Zurich	4.48	3.28	−1.94 to 10.90	1.37	.17
MA2 and 1W2	−3.67	5.17	−13.80 to 6.46	−0.71	.48
MA2 and relapse	3.99	6.31	−8.36 to 16.35	0.63	.53
1W2 group and relapse	−1.06	9.17	−19.02 to 16.91	−0.12	.91
MA2 and 1W2 group and relapse	18.93	9.24	0.82 to 37.05	2.05	.04

Abbreviation: 1W2, discontinuation between the first and second scan; MA2, second scan; ROI, region of interest; SE, standard error.

[a] Categorical variable names are binary coded such that the estimate for MA2 represents the difference in response for MA2 vs the reference category (first scan [MA1]). Interactions are denoted so that the estimate for MA2 and relapse represents the difference of the increase (from MA1 to MA2) for those who went on to relapse vs those who did not.

tients who relapsed compared to those who did not (n = 27) (point estimate, 19.15; $t_{17.99}$ = 3.1; *P* = .007). Examining the left and right amygdalae separately, we found a 3-way interaction on the right side only (right: time, discontinuation group and relapse status interaction: β, 25.68; 95% CI, 5.6 to 45.7; *P* = .02; left: time, discontinuation group and relapse status interaction: β,10.85; 95% CI, −8.4 to 30.1; *P* = .61). The increase in amygdala reactivity was significant only for the right side (point estimate, 26.4,; t_{11} = 3.7; *P* = .007). The group difference at the second assessment between those who went on to relapse vs those who did not were significant for both sides (left point estimate, 16.97; $t_{19.34}$ = 2.8; *P* = .02; right point estimate, 20.98; $t_{17.05}$ = 2.9; *P* = .02).

Association Between Amygdala Reactivity Changes and Time to Relapse

The results of the proportional hazards Cox model with the time to relapse as the right-censored dependent variable are shown in eTable 1 in Supplement 1. In the discontinuation group, the difference in amygdala reactivity (MA2 minus MA1) was associated with time to relapse: patients with greater increase in amygdala tended to relapse earlier as indicated by a significant interaction of the difference in amygdala reactivity and the discontinuation group variable with a hazard ratio of 1.05 (β, 0.05; 95% CI, 1.01-1.09; *P* = .01). Fitting models separately to each group yielded qualitatively the same results, with a significant effect of the change in amygdala reactivity (hazard ratio, 1.05; 95% CI, 1.02-1.09 for the discontinuation group only). There were no significant effects of age, sex, or site in either model.

Prediction of Relapse From Amygdala Reactivity

The predictive power of the change in amygdala reactivity between the first and second assessments (with all voxels in the ROI as features) is shown in **Figure 3**. Results for models based only on measurements at assessment 1 or assessment 2 are shown in eTable 2 in Supplement 1. We found predictive accuracies not significantly from chance for the models based on the amygdala activity of all patients at assessment 1 before discontinuation, and amygdala reactivity at assessment 2 in the discontinuation group. However, the model based on the difference between assessments 1 and 2 in amygdala reactivity (for all voxels in the bilateral ROI) yielded a predictive (balanced) accuracy of 67% (95% posterior predictive interval, 53-80; *P* = .02; left side: 58%; 95% posterior predictive interval, 45-72; right side: 71%; 95% posterior predictive interval, 57-84%). After correcting for multiple comparisons, the posterior probability for the predictive accuracy being less than 50% is less than 0.05 only for the model based on the voxels in the right ROI but not the other models.

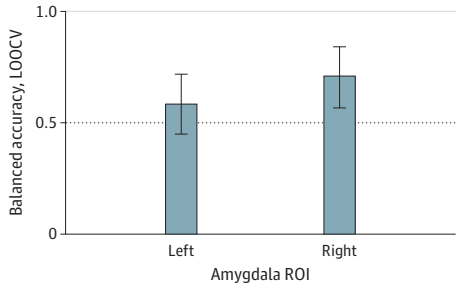
Discussion

Whether to discontinue antidepressant medication is a key clinical decision in the management of depression and brings with it a potentially substantial increase in the risk of relapse,[6,7] with few individual predictors to guide clinicians or patients in their decision-making.[5,12]

In this study, we report that an increase in amygdala reactivity to negative emotional face stimuli after antidepressant discontinuation was associated with relapse during a 6-month follow-up period. The findings are specific: the increase in amygdala reactivity following antidepressant discontinuation occurred before relapse, and an increase in amygdala reactivity was only observed after discontinuation and in those individuals who go on to relapse (n = 12 for this comparison). The increase in reactivity also appeared to be—to the extent this could be assessed within the study—potentially predictive of future relapse. These findings suggest that there is individual variation in the impact of (mostly serotonergic) antidepressant medication discontinuation on amygdala reactivity: there was no main effect of discontinuation, meaning that amygdala reactivity only increased in individuals who later relapsed. This raises the tantalizing possibility that amygdala reactivity was being maintained by antidepressant medication in some individuals and by other processes in others. Removal of antidepressant medication hence only had an adverse effect on those individuals who effectively relied on it to regulate amygdala reactivity.

Overall, the pattern of findings is consistent with the extensive literature on the relationship of amygdala reactivity, negative affective bias, and depression. The amygdala reactivity to negative emotional faces can be seen as an instance of negative affective bias, which is thought to underlie maintenance of the depressed state.[16-18,45] While still medicated, patients in remission in our sample did not differ from the control group in terms of amygdala reactivity, supporting the notion that effective antidepressant medication

Figure 3. Relapse Prediction



Depicted is the predictive accuracy of the relapse classifiers based on right and left amygdala regions of interest (ROI; ie, the modes of the posterior over the balanced accuracy inferred from the confusion matrix resulting from a leave-one-out cross-validation [LOOCV] procedure). The classifiers were based on the voxelwise increase in the face-form contrast estimates. Error bars indicate the 95% posterior predictive intervals, and the dotted line is the chance level.

treatment restores normal amygdala reactivity. This is in line with previous work showing that amygdala hyperactivity was increased in patients with depression but decreased with treatment.[20,25,30,46]

The findings add to the existing work suggesting that neurocognitive markers may have an informative role to play in predicting relapse after antidepressant discontinuation. While clinical features and even discontinuation symptoms are not predictive of relapse[13,44] in this sample, several neurocognitive measures have shown promise. For example, resting-state fMRI connectivity does change with discontinuation, and may be predictive of relapse[15] and a behavioral measure based on effort sensitivity assessed at baseline was predictive of relapse, although it was not altered by the discontinuation itself.[14] Similarly, prediscontinuation electroencephalography measures of affective reactivity are predictive of relapse, but we do not know whether this changes with discontinuation.[47]

Other work has identified abnormal processing of emotional stimuli that may be mediating a vulnerability to relapse after remission, such as frontotemporal connectivity during emotional face processing,[48] emotional reactivity[49-51] and hyperconnectivity between anterior temporal and subgenual cortices while experiencing self-blaming emotions.[3] This does not seem to be the case for amygdala reactivity in the present study. Note that the absence of such a baseline effect strengthens the interpretation of the selective association between the discontinuation and relapse in what is an observational study, albeit with a randomized component. The finding of stronger reactivity in the right amygdala is in line with previous work showing a stronger role of the right hemisphere in processing faces and suggestions that the right amygdala plays a specific role in the processing of angry and fearful facial expressions.[35,52,53]

The translational potential of the findings is uncertain. While we found that amygdala activity changes were predictive of relapse, the analyses suggest that the measurement after discontinuation is required. This clearly substantially limits its scalability. However, similar effects could potentially be observed with related pharmacological challenges (eg, during a short-term discontinuation challenge, where patients stop medication for a couple days only). This could be more practically feasible and may potentially support further treatment decisions.

Limitations

The study has a relatively small sample size (patients in the discontinuation group, 12 of whom relapsed) and the findings need to be treated with caution until they are replicated in a larger study. The costs of scaling neuroimaging studies in this setting are substantial and thus smaller-scale studies such as this one are required. The study was unblinded; both participants and experimenters knew which group participants were in and when they discontinued. As such, it is not possible to disentangle pharmacological from psychological effects of discontinuation. To achieve this, a placebo-controlled study is required.[6,7] The standard version of the task used does not allow general face processing to be disambiguated from emotion processing more specifically.

Conclusions

The AIDA study was a longitudinal, observational study with a randomized component. The design allowed 4 questions to be addressed, namely regarding the remitted but medicated depressed state, the effect of antidepressant medication discontinuation, the association between relapse and baseline features, and the association between the effect of antidepressant medication discontinuation and relapse. An increase in amygdala reactivity after antidepressant medication discontinuation was associated with risk of relapse. This adds to recent evidence that more specific neurobiological or behavioral measures can predict relapse and may hold promise for informing clinical treatment decisions around antidepressant medication discontinuation. Overall, the results of this study and previous results suggest that affective decision-making processes are engaged by the discontinuation and moderating relapse risk; however, the details will require further and larger-scale replication.

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