Human amygdala engagement moderated by early life stress exposure is a biobehavioral target for predicting recovery on antidepressants

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Amygdala circuitry and early life stress (ELS) are both strongly and independently implicated in the neurobiology of depression. Importantly, animal models have revealed that the contribution of ELS to the development and maintenance of depression is likely a consequence of structural and physiological changes in amygdala circuitry in response to stress hormones. Despite these mechanistic foundations, amygdala engagement and ELS have not been investigated as biobehavioral targets for predicting functional remission in translational human studies of depression. Addressing this question, we integrated human neuroimaging and measurement of ELS within a controlled trial of antidepressant outcomes. Here we demonstrate that the interaction between amygdala activation engaged by emotional stimuli and ELS predicts functional remission on antidepressants with a greater than 80% cross-validated accuracy. Our model suggests that in depressed people with high ELS, the likelihood of remission is highest with greater amygdala reactivity to socially rewarding stimuli, whereas for those with low-ELS exposure, remission is associated with lower amygdala reactivity to both rewarding and threat-related stimuli. This full model predicted functional remission over and above the contribution of demographics, symptom severity, ELS, and amygdala reactivity alone. These findings identify a human target for elucidating the mechanisms of antidepressant functional remission and offer a target for developing novel therapeutics. The results also offer a proof-of-concept for using neuroimaging as a target for guiding neuroscience-informed intervention decisions at the level of the individual person.

amygdala | early life stress | human brain imaging | predictive biomarkers | antidepressant remission

Amygdala reactivity and exposure to early life stress (ELS) are both strongly implicated in depression mechanisms in both animal and human models (1–6). The amygdala plays an important role in emotion processing, including evaluating biologically salient emotional stimuli, generating emotional states and potentiating emotional memories (7). It also plays a central role in the stress response, both promoting downstream hypothalamic–pituitary–adrenal (HPA) axis stimulation and receiving HPA axis feedback (8). Engagement of the stress system can fundamentally change amygdala structure and function, especially as a result of ELS (2, 9–11). Moreover, the amygdala is likely a component of the neural circuit involved in antidepressant action (12, 13), and the antidepressant response is modified by prior stress exposure (10, 14). Despite these mechanistic foundations, amygdala–stress interactions have not been investigated as a prognostic biobehavioral therapeutic target for depression.

Human neuroimaging investigations have demonstrated strong links between depression and amygdala abnormalities in both structure and function (1, 15–21). Structurally, decreased amygdala volumes were found in unmedicated depressed individuals

relative to healthy controls, whereas larger amygdala volumes were found in depressed individuals receiving antidepressant treatments (21). Functionally, distinct profiles of amygdala activation, such as hyperengagement of the amygdala to threat

Significance

Amygdala reactivity and early life stress (ELS) are both strongly implicated in the mechanisms of depression in animal and human models. Despite these mechanistic foundations, amygdala reactivity and ELS have not been investigated as biobehavioral targets for predicting functional remission in depression. We addressed this issue by integrating human imaging and ELS measures within a controlled trial of antidepressant outcomes. We demonstrate that the interaction between ELS and amygdala engagement predicts functional remission on antidepressants with a greater than 80% cross-validated accuracy. In depressed people exposed to high ELS, a greater likelihood of remission was predicted by amygdala hyperreactivity to socially rewarding stimuli, whereas for those with low-ELS exposure, amygdala hyporeactivity to both rewarding and threat-related stimuli predicted remission.

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and hypoengagement to positive emotion, have been reported in depression (16–19).

Animal models have further highlighted the importance of the amygdala in the pathophysiology of depression and the mechanisms underlying this association. For example, stress paradigms that induce depressive-like behaviors result in hypertrophy of the amygdala, potentially through an increase of dendritic arborizations and spines (1, 9). Parallel physiological changes contribute to a sensitization of amygdala engagement (9). Independently, direct stimulation of the amygdala is sufficient to induce an increase in emotional reactivity and fear-like behaviors (22). These amygdala-mediated behaviors, together with decreased emotional control by medial prefrontal cortex regions, are thought to contribute to the increased negative bias and overly negative evaluation of the self that are fundamental features of human depression (23). Although these rodent models can reproduce depressive-like behaviors, they cannot capture the personal human experience of depression, making it difficult to directly translate findings between animal and human models. Despite this limitation, animal models have significantly aided our understanding of the neural mechanisms by which depression develops. In particular, these models have provided critical insights into a mechanistic pathway through which stress, especially ELS, produces the cascade of neurobiological changes that disrupt emotion regulation and generate depression in adulthood (1, 24, 25).

Similarly, in humans, a history of ELS, particularly abuse or neglect, is a prominent risk factor for developing depression and exacerbating depression severity (3, 4). Mechanisms by which ELS affects adult psychopathology are thought to involve—at least in part—engagement of the HPA axis in the immediate response to the stressor (2, 6, 10, 11, 19, 26). This engagement of the HPA axis and release of stress-related hormones are, in turn, believed to cause structural and functional changes in the neural circuits that underlie emotion processing. The amygdala is one of the most consistently reported regions demonstrating such changes (1, 9, 27). These structural changes outlast the termination of the stressor (9), and may heighten emotional reactivity and fundamentally alter the way these neural circuits respond to subsequent stressors (9).

Not all individuals who experience ELS develop depression. The cumulative risk likely depends on the interaction between the stressor and the degree to which the stressor impacts emotional brain circuits. For example, in rodents, the degree of amygdala hypertrophy resulting from an initial stressor differentiates rodents that go on to develop depressive-like behaviors following a subsequent stressor from those that do not (28). That is, subsequent maladaptive sensitivity to stress depends on the degree to which the early stressor impaired the amygdala. Similarly, in humans, the interaction between the degree of amygdala engagement at baseline and the amount of subsequent stress predicts which people developed an internalizing disorder, including depression, 1–4 years later (29).

Amygdala function and ELS have independently been identified as factors contributing to antidepressant response. Evidence from rodents and humans has implicated the amygdala as a target of antidepressants (12, 13). Congruent with this framework, amygdala engagement in response to both positively and negatively valenced stimuli distinguished antidepressant responders and nonresponders (30). Specifically, preintervention amygdala hypoengagement in response to subliminal fearful and angry faces (a signal of potential threat) and happy faces (a signal of social reward) have separately been associated with better antidepressant response. Moreover, amygdala reactivity in responders to both negatively and positively valenced stimuli increased toward normalization following antidepressant intervention (30). Increasing levels of ELS have also been associated with poorer outcomes to pharmacotherapy, pharmacotherapy combined with psychotherapy, and psychotherapy alone (4, 5, 14).

In summary, these overlapping lines of evidence have demonstrated that: (*i*) amygdala engagement and ELS independently contribute to antidepressant response, (*ii*) functional and structural

alterations in amygdala circuitry can result as a function of ELS, and (*iii*) vulnerability to developing depression depends on the interaction between amygdala function and ELS rather than either alone. However, despite these findings, no study has tested whether the interaction of amygdala engagement and ELS could be used as targets for therapeutic response to antidepressants in humans. Addressing this question could provide a new mechanistic understanding for why some individuals respond to antidepressant treatments and others do not, as well as offer new targets for intervention. Given that (*i*) a large societal cost is associated with untreated depression, (*ii*) less than a third of individuals typically remit after first-line antidepressants, and (*iii*) there is currently no test available for predicting remission in practice, these findings have important clinical ramifications.

In the present study, we hypothesized that an individual's capacity to remit after an antidepressant intervention would depend on ELS history and amygdala reactivity to fearful and happy faces. Defining remission as requiring functional improvement and alleviation of symptoms (31), we tested the following hypotheses:

Hypothesis 1: Combining measures of ELS and preintervention amygdala reactivity to happy faces will predict functional remission better than ELS or amygdala reactivity alone.

Hypothesis 2: Combining measures of ELS and preintervention amygdala reactivity to fearful faces will predict functional remission better than ELS or amygdala reactivity alone.

Hypothesis 3: Combining measures of ELS and amygdala reactivity to both happy and fearful faces will provide the most accurate prediction of functional remission, beyond predictions based on ELS or specific stimulus valence-evoked amygdala reactivity alone.

Results

Participant Characteristics. Of 102 participants with major depressive disorder (MDD) imaged, 22 dropped out. Eighty were assessed at week 8, of which 10 had no ELS data available. Baseline demographic, clinical breakdown, and dosage information for the three antidepressants are presented in Tables S1 and S2 for the analyzed sample ($n = 70$) split by ELS status and remission type. Those who achieved "functional remission" (i.e., symptoms returning to healthy range plus functional improvement) and those who did not showed no detected differences in age, education level, duration of MDD episode, social/occupational functioning, depression symptoms, or dose within each treatment arm. This lack of differences remained when further stratified by level of ELS exposure (all $P > 0.05$).

Predictors of Functional Remission. Fig. 1 and Table 1 show the performance of each classification model with and without leave-one-out cross-validation in predicting functional remission.

Covariate Model. To serve as a basis of comparison for more complex models, a regression model consisting solely of clinical and demographic variables was used to classify functional remission (Table S3). In the first step, age, years of education, baseline depression severity, and MDD episode duration were included as predictors based on their previous associations with treatment success (30, 32). This model overall showed a trend toward significance ($\chi^2 = 73.07$, df = 4, $P = 0.067$) (Table S3). Receiver operating characteristic (ROC) analyses revealed an area under the curve (AUC) of 0.71 with 84% sensitivity and 59% specificity (Fig. 1*A* and Table 1).

Consistent with prior findings (4, 5, 14), adding ELS to the model significantly increased overall performance ($\Delta\chi^2 = 5.88$, Δdf = 1, $P = 0.025$) (Table S3). Within this model, the likelihood of achieving functional remission was negatively associated with ELS status [unstandardized beta coefficient (B) = −0.99, Wald statistic (W) = −2.12, $P = 0.034$] when holding covariates at a fixed
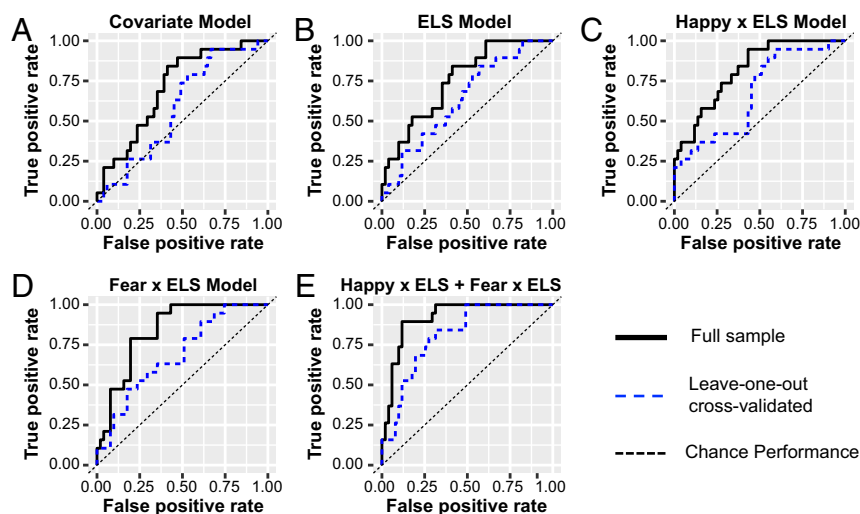
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Fig. 1. ROC curves showing the relative performance of candidate regression models in predicting functional remission. ROC curves model performance in predicting functional remission for 70 participants using the following predictors: (*A*) demographic/clinical measures; (*B*) demographic/covariate measures and ELS; (*C*) demographic/covariate measures and the interaction between amygdala reactivity to happy faces and ELS; (*D*) demographic/covariate measures and the interaction between amygdala reactivity to fearful faces and ELS; and (*E*) demographic/clinical covariates, the interaction between ELS and amygdala reactivity to happy faces, as well as the interaction between ELS and amygdala reactivity to threatening faces.

value. ROC analyses demonstrated that this model performed modestly in predicting functional remission: AUC of 0.75; sensitivity of 84%; and specificity of 59% (Fig. 1*B* and Table 1). These metrics dropped to 0.64, 95%, and 39%, respectively, using a leave-one-out cross-validation (Table 1).

Happy × ELS Model. We next tested whether models combining ELS and amygdala reactivity to happy faces would significantly increase model performance (see details in *SI Results* and Table S4). Briefly, the model that included interactions between ELS and amygdala reactivity to happy faces performed significantly better than the model with ELS and amygdala reactivity without interactions, even at a conservative Bonferroni level ($\Delta\chi^2 = 8.03$, df = 1, $P = 0.005$) (Table S4). The interaction model classified functional remission with an AUC of 0.82, sensitivity of 95%, and specificity of 57% (Fig. 1*C* and Table 1). Leave-one-out cross-validation analyses yielded an AUC of 0.69, sensitivity of 89%, and specificity of 45%, suggesting some caution in making inferences about its generalizability (Fig. 1*C* and Table 1).

Fear × ELS Model. We then tested whether models combining ELS and amygdala reactivity to fearful faces would significantly increase

model performance beyond each independently (see details in *SI Results* and Table S4). Briefly, the fear reactivity × ELS interaction model performed only marginally better than a model with fear reactivity and ELS without their interaction ($\Delta\chi^2 = 3.04$, df = 1, $P = 0.081$) (Table S4). The fear reactivity × ELS model had an AUC of 0.84, sensitivity of 95%, and specificity of 65% (Fig. 1*D* and Table 1). The leave-one-out cross-validation model was relatively weaker, with an accuracy of 0.72, sensitivity of 47%, and specificity of 90%, suggesting caution in making inferences about its generalizability (Fig. 1*D* and Table 1).

Happy × ELS + Fear × ELS. We tested whether combining the additive and interaction effects between ELS, happy reactivity, and fear reactivity would further increase model performance. We focused specifically on the interaction models because both the happy and fear interaction models performed better than the additive models, especially for happy. As predicted, the combined model had additive effects in predicting functional remission ($\chi^2 = 47.10$, df = 9, $P < 0.001$) (Table S4). Adding the fear–ELS and happy–ELS interactions to a model that contained the happy reactivity, fear reactivity, and ELS (as well as covariates) significantly increased the ability to predict functional remission at the Bonferroni-corrected

Table 1. Model performance summary

Model	Covariates*	ELS	Happy × ELS	Fear × ELS	Happy × ELS + fear × ELS
Full sample					
AUC	0.71	0.75	0.82	0.84	0.92
Sensitivity (chance rate)	0.84 (50)	0.84 (50)	0.95 (50)	0.95 (50)	0.89 (50)
Specificity (chance rate)	0.59 (50)	0.59 (50)	0.57 (50)	0.65 (50)	0.88 (50)
PPV (remission rate)	0.91 (27)	0.91 (27)	0.97 (27)	0.97 (27)	0.96 (27)
NPV (nonremission rate)	0.43 (73)	0.43 (73)	0.45 (73)	0.50 (73)	0.74 (73)
Leave-one-out cross-validated					
AUC	0.59	0.64	0.67	0.69	0.81
Sensitivity (chance rate)	0.95 (50)	0.84 (50)	0.94 (50)	0.47 (50)	0.84 (50)
Specificity (chance rate)	0.33 (50)	0.43 (50)	0.41 (50)	0.82 (50)	0.69 (50)
PPV (remission rate)	0.94 (27)	0.88 (27)	0.95 (27)	0.80 (27)	0.92 (27)
NPV (nonremission rate)	0.35 (73)	0.36 (73)	0.38 (73)	0.50 (73)	0.50 (73)

NPV, negative predictive value; PPV, positive predictive value.
*Covariates include age, years of education, baseline depression severity, and MDD episode duration.

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level ($\Delta\chi^2 = 14.91$, df $= 2$, $P < 0.001$) (Table S4). The combined model increased the AUC to 0.92, while maintaining high sensitivity (89%) and specificity (88%) (Fig. 1E and Table 1). The leave-one-out cross-validated model similarly maintained high AUC (0.81), sensitivity (84%), and specificity (69%), suggesting good generalizability (Fig. 1E and Table 1). We replicated these results using an alternate analytical approach that uses the total number of ELSs rather than the interval scale measure (*SI Results* and Table S5).

Within this full model, the happy–ELS ($B = 2.78$, $W = 2.70$, $P = 0.007$) and to a lesser extent the fear–ELS ($B = 1.53$, $W = 1.94$, $P = 0.052$) interactions contributed to the prediction. The slope of the relationship between the likelihood of functional remission and amygdala reactivity to both happy and fearful faces became increasingly positive with greater ELS, as computed by our statistical model at mean levels of other predictors. Thus, those with low ELS were predicted to have a greater probability of remitting if they had less baseline amygdala reactivity to both happy ($B = -2.96$, $W = -2.53$, $P = 0.011$) and fearful ($B = 3.00$, $W = -2.53$, $P = 0.011$) faces (Fig. 2), whereas for the mid-ELS group, remission was associated with amygdala reactivity to fearful faces (but not happy faces) such that those with the lowest amygdala reactivity were the most likely to remit (fear: $B = -1.47$, $W = -2.33$, $P = 0.020$; happy: $B = -0.19$, $W = -0.34$, $P = 0.732$). In contrast, the model estimated that those with high ELS were more likely to remit with increasing preintervention amygdala reactivity to happy faces ($B = 2.57$, $W = 2.11$, $P = 0.027$) but showed no association with fear reactivity ($B = 0.06$, $W = 0.08$, $P = 0.940$). The predicted likelihood of remission as a function of amygdala reactivity to both fearful and happy faces across ELS groups is plotted in Fig. 2.

Clinical Translational Relevance. Due to our combined model's high degree of accuracy, it is relevant to consider its applicability to the clinical setting. Although our results remain speculative, we have demonstrated that in a moderate-sized sample, a single metric may be derived from our combined logistic regression model and used to support decisions about individual patients. In the happy × ELS + fear × ELS model, ROC analyses determined that a log-odds cross-validated threshold of −0.80 (the average threshold across all leave-one-out folds) could be used to distinguish remitters from nonremitters within this sample with a sensitivity of 60% and specificity of 80%. In future applications, a history of ELS coupled with an amygdala scan may be used to identify likely nonremitters (those below the −0.80 threshold; Fig. 2) before beginning a potentially ineffective pharmacotherapy.

Discussion

Our study demonstrates that functional remission with antidepressants may be dependent not only on an individual's ELS history and degree of amygdala engagement during facial emotion viewing tasks independently but on their interaction. Given this information, we could predict with a high degree of accuracy (81%) who would and would not functionally remit following pharmacotherapy with commonly prescribed antidepressants. Given that both amygdala circuitry and ELS are also strongly implicated in the neurobiology of depression, our predictive model provides a potential clinically meaningful target for mechanistic investigations and for novel intervention development.

Previous independent lines of research have shown how both ELS and amygdala reactivity may independently contribute to the pathophysiology of development, maintenance, and functional remission in depression. ELS has been shown to moderate antidepressant outcomes (4, 5, 14, 30). Consistent with these reports, we found that the severity of exposure to ELS in childhood is associated with a greater likelihood of treatment failure across three commonly prescribed antidepressants. Similarly, and consistent with previous evidence for the independent role of amygdala reactivity in predicting antidepressant remission (30), our model suggests that amygdala hyporeactivity to subliminally presented fearful faces may be associated with better functional remission when not controlling for ELS. Our study combines these two lines of investigation to demonstrate that the functional alterations in amygdala circuitry, potentially as a result of stress-induced plasticity, may be moderating the impact of ELS on functional remission.

The present findings advance our current knowledge by demonstrating that information on amygdala function and interactions with exposure to ELS together may be used to form the most accurate predictive model for antidepressant remission, even in a moderate-sized sample. When considering degree of ELS exposure and amygdala functioning together, we identified several
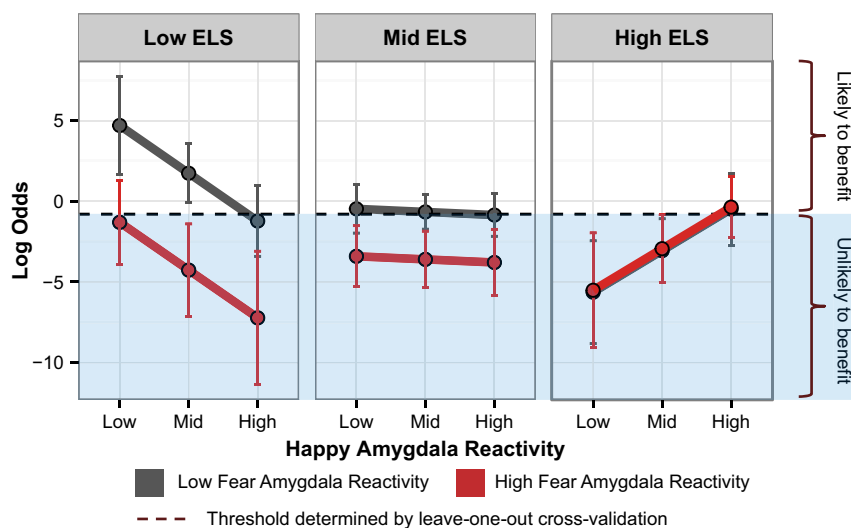
Fig. 2. Binary classification of remission. Predicted likelihood of remission (log odds) at varying levels of ELS and amygdala reactivity to emotional faces. The likelihood of remission was generated from the model containing both the interaction between ELS and amygdala reactivity to happy faces and the interaction between ELS and amygdala reactivity to fearful faces, using all 70 participants. The likelihood of remission was calculated at mean levels of covariates at low (mean minus 1 SD), mid (mean), and high (mean plus 1 SD) levels of reactivity to happy faces, as well as low and high levels of reactivity to fearful faces. Individuals with predicted probabilities above the cross-validated threshold for classification (dotted line) would be classified as likely to respond to escitalopram, sertraline, or venlafaxine, whereas those below would not. Error bars show 90% confidence intervals.

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preliminary patterns of amygdala reactivity that were associated with likelihood of remission and dependent on ELS status. For example, our results suggest a negative relationship between amygdala reactivity to both fearful and happy faces and the likelihood of achieving functional remission in individuals with low levels of ELS. That is, for individuals free of ELS, our model would predict a greater likelihood of remission if they showed neural insensitivity to salient emotion, reflected in hypoengagement in response to both threatening and socially rewarding stimuli. It is possible that these individuals, in the absence of stress sensitization, can benefit most from the impact of antidepressants on amygdala circuits. This result is consistent with a prior study demonstrating that antidepressants can normalize amygdala function by increasing amygdala reactivity to both happy and fearful faces (30) in those individuals who responded to treatment. Those with low ELS but hypersensitivity to threat might be candidates for psychosocial interventions that focus on improving emotion regulation [e.g., dialectical behavior therapy (33)] or prosocial behaviors (34).

Our results suggest that individuals with a high-ELS exposure would have a greater likelihood of functional remission with antidepressants if they had a preexisting hyperengagement in response to socially rewarding stimuli, relatively independent of how they respond to fearful faces. The neurobiological consequences of ELS are believed to arise initially as an adaptive response to the current environmental stressors. For example, in an abusive environment, an increased sensitivity to threat-related emotional signals may enable earlier detection and a potentially increased ability to avoid a negative confrontation with the caregiver (35). However, these short-term benefits are proposed to be associated with long-term functional and structural changes of limbic-related brain regions—perhaps most notably in the amygdala—that manifest as a function of the severity of the ELS exposure (1, 9, 27, 36, 37). Consistent with this framework, in childhood, the severity of ELS exposure has been positively associated with amygdala reactivity to both threatening and happy faces in a dose-dependent manner (26, 38). Similarly, as adults, the severity of prior stress exposure has also been associated with amygdala engagement in response to threatening faces (19). However, for happy faces, there was a marginally significant negative relationship such that greater ELS severity was associated with a lower amygdala response to happy faces (39). Taken together, these findings suggest that whereas initially ELS boosts sensitivity for salient expressions that encompass both positive and negative emotions, later in life this may progress into a bias toward threat-relevant stimuli, potentially with decreased sensitivity to happy faces. It is possible that "high-ELS exposure" individuals who are able to maintain amygdala hyperengagement to socially rewarding stimuli are endowed with additional resilience factors that enable them to mount a more effective response to antidepressants (37).

Although additional replication is required, these findings suggest that targets of antidepressant response may (at least in part) be tied to the neurobiology of depression itself. This study also makes a leap forward in demonstrating the possibility of a single composite brain-stress predictive metric relevant to informing therapeutic decisions that may be derived and used before fully understanding underlying neural mechanisms. Such a metric also offers a viable target for future mechanistic investigations and for studies aimed at developing novel interventions. Moreover, these findings provide additional support for the need to consider a life-course approach to the prevention and treatment of mental disorder (40).

Findings from this study should be appreciated within the context of certain limitations. Although our study sample would be considered large for neuroimaging measures and represents a statistical advance in power from the few previous neuroimaging prediction studies, it is relatively small when stratifying by ELS subgroups. Although we have undertaken steps to demonstrate the generalizability of our findings, including using cross-validation techniques and replicating our findings using an alternate analytical approach (*SI Methods*), replication and assessment of generalizability in an independent sample would be an important next step.

Due to stratifying the sample by ELS, our analyses were not sufficiently powered to test whether the ELS interactions with amygdala reactivity predictions would be further dependent on the specific type of antidepressant therapy. Future investigations are needed to determine whether the interaction between ELS and amygdala reactivity is a differential predictor of antidepressant outcomes. Finally, due to the practical trial design, the study was necessarily limited to antidepressants in common use in each of the participating countries. It would similarly be important to verify the predictive role of ELS and amygdala reactivity with additional antidepressants and second-generation antipsychotics with antidepressant actions that have distinct mechanisms of action, as well as psychotherapy.

Our results advance our understanding of how ELS and amygdala engagement function synergistically to predict subsequent remission from depression with antidepressants. Moreover, we have demonstrated that a single brain-stress metric may be derived from our predictive model and used to support decisions about individual patients. In short, metrics based on combined brain and life experience data hold promise for developing a neuroscience-informed approach to mental disorder and its management.

Methods

Overview and Study Design. Functional imaging data were obtained from 102 participants from the International Study to Predict Optimized Treatment in Depression (iSPOT-D). For a complete description of the randomized iSPOT-D practical trial protocol, clinical assessments, inclusion/exclusion criteria, and diagnostic procedures, see Williams et al. (41). In short, the primary diagnosis of nonpsychotic MDD was confirmed using the Mini-International Neuropsychiatric Interview (42), according to *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (DSM-IV) criteria (43), and inclusion criteria included a score of $\geq$16 on the 17-item Hamilton Rating Scale for Depression (44) (HRSD$_{17}$). Sample size and power were determined as part of the protocol development (45).

All participants were either antidepressant medication-naïve or underwent a washout period of at least 1 wk (five half-lives). Participants were randomly assigned using Phase Forward's validated, web-based interactive response technology to receive escitalopram, sertraline, or extended-release venlafaxine.

This study was conducted according to the principles of the Declaration of Helsinki 2008. After the study procedures were fully explained in accordance with the ethical guidelines of the Western Sydney Area Health Service Human Research Ethics Committee, participants provided written informed consent.

Early Life Stress. ELS was assessed using the 19-item Early Life Stress Questionnaire, which assesses exposure to abuse, neglect, family conflict, illness/death, and natural disasters before 18 y of age (46). Participants were split into low- ($\leq$1 event), mid- (2–5 events), and high- ($\geq$6 events) ELS groups. These groups did not differ in demographic factors (all $P > 0.05$; see Table S1 for ELS distribution details).

Criteria for Functional Remission. Because childhood adversity produces depressive-anxious symptoms as well as stress-related adjustment problems, we defined functional remission by a combined measure of clinician-rated depression symptom severity using the HRSD$_{17}$ (44), self-reported symptom severity using the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR$_{16}$) (47), and observer-rated functional capacity using the Social and Occupational Functioning Assessment Scale (SOFAS) (48) at week 8. Remitters were defined as being in the normative range of symptoms ($\leq$7 on the HRSD$_{17}$ and $\leq$5 on the QIDS-SR$_{16}$) and with healthy adjustment ($\geq$10-point improvement from baseline to achieve $\geq$61 on the SOFAS).

Functional MRI Emotion Paradigm. Amygdala reactivity to happy and fearful faces was assessed relative to neutral comparison faces using an established masking paradigm (30). Stimuli were drawn from a standardized series of facial expressions (49) modified to be centrally positioned at eye level. Details of the MRI acquisition, preprocessing, and stimuli presentation have been published previously (30) and can be found in *SI Methods*.

Statistical Analyses. Hierarchical logistic regression models and ROC analyses implemented in R (50) were used to test the predictive performance of models including ELS and amygdala reactivity measures for functional remission. (Here we define hierarchical regression as a series of successive logistic regression models, adding additional predictors with each step. This is not to be confused with hierarchical linear models, which are used in modeling nested data.) The

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Wald statistic was used to determine the significance of the contribution of each predictor. To account for multiple statistical tests, we report significance for our six tests at a $0.05/6 \leq 0.008$ Bonferroni-corrected level (three additive and three interactive tests).

To increase the generalizability of the model predictions and reduce the bias caused by model fitting (51), leave-one-out cross-validation was used to derive an unbiased threshold that could be prospectively used to classify remitters versus nonremitters as well as assess the generalizability of the ROC performance metrics. The specific steps of each analysis are detailed in *SI Methods*. ROC curves were drawn using the Epi package of R (52).

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