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Sequential decreases in basolateral amygdala response to threat predict failure to recover from PTSD

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Amygdala hyperreactivity early-post trauma has been a demonstrable neurobiological correlate of future posttraumautic stress disorder (PTSD). The basolateral amygdala (BLA) particularly is vital for fear memory and threat processing, but BLA functional dynamics following a traumatic event are unexplored. BLA reactivity to threat may be a trait that can predict PTSD and persist over time. Alternatively, BLA responsivity to threat cues may change over time and be related to PTSD severity. As part of a larger, multisite study, AURORA, participants 18–75 years old were enrolled in an emergency department (ED) within 72 h of a traumatic event ($N = 304$, 199 female). At 2-weeks and 6-months post-trauma, PTSD symptoms, BLA responses to threat (fearful>neutral faces), and functional connectivity (FC) during fMRI were assessed. Generalizability of findings was assessed in an external replication sample of ED patients ($n = 33$). Two weeks post-trauma right BLA reactivity positively predicted later PTSD severity. However, left BLA reactivity to threat at 6 months post-trauma was negatively associated with PTSD severity at that timepoint (ΔPseudo-$R^2 = 0.04$, IRR = 0.38, $p < 0.001$). In addition, a decrease in BLA reactivity from 2-weeks to 6-months predicted greater PTSD severity at 6 months (ΔPseudo-$R^2 = 0.03$, IRR = 0.58, $p < 0.001$). This replicated in the external sample. A reduction in left BLA FC with the dorsal attention network predicted increased PTSD severity over time. These findings support a shift in BLA function within the first 6 months post-trauma that predicts PTSD pathology and stand in contrast to prior conceptualizations of amygdala hyperreactivity as a trait-like PTSD risk factor.

Neuropsychopharmacology; https://doi.org/10.1038/s41386-025-02115-1

INTRODUCTION

Of adults who experience a traumatic event, most will naturally recover from initial symptoms of traumatic stress [1–3]. Yet, approximately 17% will maintain chronic post-traumatic stress disorder (PTSD) symptomology in the months following their trauma [4]. Identifying biological factors that accompany recovery versus PTSD symptom maintenance is of great importance in crafting interventions to improve treatment options and predict mental health trajectories.

Although the symptom presentation of PTSD can vary across individuals, many neurobiological models hypothesize PTSD to be a disorder of disrupted threat processing [5, 6]. Of neurobiological factors implicated in PTSD, few have received as much attention as the amygdala [7–13], a brain region involved in threat processing and fear memory encoding [14–17]. Amygdala hyperreactivity to threat is highly reported in individuals with PTSD [9, 11, 18, 19], although hyporeactivity is also reported in relation to dissociative symptomology [20–22]. Both hyperreactivity and hyporeactivity are potentially influenced by disrupted modulatory signals from regions encompassed by the prefrontal cortex (PFC) - such as the ventral medial PFC (vmPFC), rostral anterior cingulate cortex (ACC), and dorsal ACC - and the hippocampus, demonstrated in response to threat presentation, trauma-related scripts, and during resting state [12, 23–25]. These areas are believed to synapse in the basolateral amygdala (BLA) [26–28]. The BLA plays a crucial role in regulating threat responses, such that it incorporates cortical and sensory information related to threat cues, thereby influencing fear memory and threat perception in PTSD [5, 26–29]. A number of PTSD-related findings have been isolated to the BLA, including greater BLA responses to negative scenes [14], and greater resting state functional connectivity (FC) of the BLA-dorsal medial PFC, vmPFC, and the -pregenual and -dorsal anterior cingulate cortex [30, 31]. This makes the BLA an a priori region of interest in studying PTSD.

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Received: 9 July 2024 Revised: 14 April 2025 Accepted: 17 April 2025
Published online: 03 May 2025

What remains unclear is how the dynamics of BLA reactivity over time relate to the longitudinal progression of PTSD symptoms. Because stress-related disorders are the only category of diagnoses that start with an index event, the timeline of recovery - or failure to recover - is a defining element of this disorder [1–3]. Longitudinal changes in the neural processing of threat cues following trauma are critical to many theoretical conceptualizations of PTSD, particularly learning and memory-related models [32–34]. However, few longitudinal studies have evaluated the neural processing of threat cues over multiple timepoints following a traumatic event. Predictive biomarker studies evaluating early neuroimaging predictors of later symptoms suggest that amygdala hyperreactivity to threat pre-trauma [18, 35] and early post-trauma [36] predicts PTSD months later following a traumatic event. However, only a single study has evaluated how neural responses to threat cues change longitudinally with respect to trauma: in a military cohort, amygdala reactivity increased from pre- to post-combat in response to fearful and angry faces [37]. Furthermore, this hyperactivation returned to pre-deployment levels by 1.5 years post-deployment, suggesting that some plasticity had occurred, potentially reflecting recovery [37, 38]. Similarly, following the successful treatment of PTSD, resting-state BLA-orbitofrontal cortex FC increases, suggesting that improved top-down control of the amygdala may accompany symptom decreases [39]. These studies suggest that, following a major stressor, most individuals experience a heightened amygdala response. For most who go on to recover, this response dies down. Although not yet tested empirically, it follows logically that individuals with greater amygdala reactivity early post-trauma, and who maintain high amygdala reactivity over time, may maintain chronic PTSD symptoms over the months following the event.

In this study among adult emergency department (ED) patients who suffered an acute traumatic event, we investigated early post-trauma BLA reactivity to social threat cues, and how this reactivity changes over time in the 6 months following that event, based on a priori hypotheses. We considered two hypothesized frameworks for the relationship between left and right BLA function and PTSD symptom change: one, that BLA reactivity to threat is a trait that can predict PTSD severity and is maintained or persists over time [40–42]; and two, that the BLA reactivity to threat cues may change over time (increase or decrease) with impacts on PTSD severity [39, 43]. Exploratory whole-brain analyses were conducted across timepoints. We additionally examined changes in the FC of the BLA over time to identify brain circuit-level dynamics that may correlate with symptom recovery, hypothesizing we would see shifts in vmPFC and hippocampal FC [12, 23–25].

MATERIAL AND METHODS

Discovery cohort

Participants and experimental procedures. Between September 2017 and July 31, 2020, $n = 2626$ participants were recruited for the AURORA study. The full recruitment protocol for this multi-site study is described previously [44]. Briefly, participants were enrolled within 72 h of an acute traumatic event during their presentation for care in one of the study EDs. The acute traumatic event involved actual or threatened serious injury, sexual violence, or death, either by direct experience, witnessing it, or learning about it. All participants were 18–75 years of age, English-speaking, and were required to have their own smartphone with internet access and an email address. Written informed consent was obtained while in the ED, and all study procedures were approved by each site's institutional review board. Exclusion information can be found in Supplementary Materials.

At a planned delay of 2 weeks (Scan 1, actual delay $M = 21.9$, $SD = 7.22$ days, range= 7–44 days) and 6 months (Scan 2, $M = 211.39$, $SD = 14.15$ days, range= 183–257 days) following the index trauma, a subset of participants visited one of five scanner sites for MRI neuroimaging visits. Of the participants from the parent AURORA study, the final MRI sample after quality control included $n = 304$ scans at 2 weeks post trauma (199 female, age $M = 33.5$), and $n = 99$ of these who also had scans at 6 months post trauma (69 female, age $M = 36.2$). A flow chart detailing the quality criteria for inclusion in these analyses can be found in *Supplementary Materials* (Fig. S1). Table 1 outlines demographic and trauma-specific aspects of the participants. fMRI responses were collected during a fearful vs. neutral faces task, designed to measure reactivity to social threat cues. This same task is shown to reliably engage amygdala, insula, and ventral visual regions in prior studies completed with trauma-exposed participants [12, 36, 45]. Participants passively viewed static fearful and neutral face stimuli presented in blocks of eight trials, with a total of 30 blocks (15 fearful, 15 neutral). During rest periods, participants were instructed to relax with their eyes open and attend to

Table 1. Clinical and demographic information of the discovery cohort.

	Week 2 Timepoint	Month 6 Timepoint
	$N = 304$	$N = 99$
Sex, female/male	199/105	69/30
Age, mean (SD)	33.5 (12.4)	36.2 (13.0)
Site (%)		
McLean	119 (39%)	38 (38%)
Wayne State University	80 (26%)	34 (34%)
Temple University	77 (25%)	23 (23%)
Washington University in St. Louis	21 (7%)	4 (4%)
Emory University	7 (2%)	0 (0%)
Race/Ethnicity (%)		
Non-Hispanic Black	139 (45.7%)	45 (45%)
Non-Hispanic White	97 (32%)	34 (34%)
Hispanic	55 (18%)	15 (15%)
Non-Hispanic other	12 (4%)	4 (4%)
Not reported	1 (0.3%)	1 (1%)
Education		
Doctoral degree	1 (0.3%)	1 (1%)
Master's degree	2 (0.7%)	0 (0%)
Some graduate school	17 (6%)	7 (7%)
Bachelor's degree	50 (16%)	13 (13%)
Associate's/some college	123 (40.3%)	47 (47%)
High school degree or below	111 (37%)	31 (32%)
Trauma type (%)		
Motor vehicle collision	221 (73%)	77 (77%)
Physical assault	34 (11%)	12 (12%)
Fall >10 ft	4 (1%)	1 (1%)
Fall <10 ft	14 (5%)	4 (4%)
Mass event	1 (0.3%)	0 (0%)
Burn	1 (0.3%)	1 (1%)
Other	17 (6%)	4 (4%)
Psychoactive medication use (%)	69 (22.7%)	18 (18%)
2-week PCL-5, mean (SD)	30.7 (17.4)	28.0 (17.4)
2-week probable PTSD (%)	130 (42.7%)	37 (37%)
6-month PCL-5, mean (SD)	21.9 (18.2)	22.0 (17.6)
6-month probable PTSD (%)	86 (28.3%)	25 (25%)

The PTSD Symptom Checklist for DSM-5 (PCL-5) Range: 0–80.
Probable PTSD: PCL-5 score >31.

white fixation cross displayed on a black background. Further details can be found in the *Supplementary Materials*.

In the ED and both scan visits, participants completed questionnaires to assess prior history and symptoms related to the ED index trauma. The PTSD Symptom Checklist for DSM-5 (PCL-5) [46] was used to assess for the presence of PTSD symptoms. An abbreviated Childhood Trauma Questionnaire (CTQ) [47], was used to assess the presence of childhood maltreatment. The Brief Dissociative Experiences Scale (DES-B) – Modified [48, 49], was used to assess the presence of dissociative symptoms. Additional information regarding questionnaires and psychoactive medication usage can be found in *Supplementary Materials*.

MRI acquisition and preprocessing. Brain imaging data were acquired on five Siemens 3 Tesla MRI systems using the EP2d-BOLD sequence for functional scans and a MPRAGE T1-weighted (T1w) image with navigation (Siemens WIP 711) for structural scans. Detailed information on the five MRI scanners, scanner-specific sequence parameters, and preprocessing are included in *Supplementary Materials* (Sequence parameters: Table S1). Briefly, structural images were assessed for quality using MRIQC [50], followed by visual inspection for anatomical abnormalities. Preprocessing was performed using FMRIPREP version 1.2.2 [51], a Nipype [52] based tool, for the Discovery cohort.

Conceptual replication cohort. $N = 33$ participants (Table 2**)** were recruited from a larger Emergency Department (ED) study. All were ED patients at Grady Memorial Hospital in Atlanta, GA, who experienced a traumatic event within 24 h of arriving in the ED. Exclusion information can be found in *Supplementary Materials*. Participants provided written informed consent for all parts of the study, and study procedures were approved by the Institutional Review Boards of Emory University and Grady Memorial Hospital. Full questionnaire collection, fMRI acquisition, and preprocessing information can be found in *Supplementary Materials*. PTSD symptom severity in response to the index trauma was measured utilizing the PTSD Symptom Scale (PSS) [53]. fMRI sessions were completed approximately 1 month (Scan 1) and 6 months (Scan 2) after ED enrollment and the acute traumatic event. fMRI responses were collected during the same social threat task (fearful vs. neutral faces) that was used in the AURORA discovery cohort.

Statistical modeling. Statistical modeling was conducted in SPM12. Blocks of fearful and neutral stimuli were modeled with separate boxcar functions representing the onset and 8000 ms duration of each block, convolved with a canonical hemodynamic response function. Individual level contrasts were constructed for fearful>neutral face blocks, with white matter, cerebral spinal fluid and global signal time-courses included as nuisance regressors. The left and right BLA regions of interest (ROIs) were defined using anatomical boundaries defined by California Institute of Technology high-resolution in vivo amygdala atlas (See *Supplementary Methods)* [54]. The mean fearful>neutral contrast estimate across all voxels in the left and right BLA mask was extracted using rex (RRID: SCR_002532), and exported for further analyses in R. The fearful>neutral contrast was utilized to measure emotional response while controlling for more basic perceptual effects of faces.

Modeling, assumption checking, and statistical thresholds are detailed in the *Supplementary Methods*. Whole-brain analysis was used to confirm task-related activation of the BLA (See *Supplementary Methods*).

Relationship between 2-week and 6-month BLA ROI reactivity and PTSD symptoms. To address the hypothesis that BLA reactivity would predict later PTSD symptom severity, and that greater BLA reactivity would accompany greater PTSD severity across timepoints, regression models tested whether threat reactivity in the left and right BLA ROI predicted concurrent or future PCL-5 scores, above and beyond covariates.

Longitudinal change in BLA ROI reactivity and PTSD symptoms. To test the hypothesis that an increase or maintenance of BLA reactivity over time would accompany increases or maintenance of PTSD severity across timepoints, regression models including change in BLA ROI reactivity (Scan 2–Scan 1 reactivity) and change in PTSD severity scores (Scan 2–Scan 1 symptoms) were used. This primary hypothesis was tested both in the Discovery and Replication cohorts. All models covaried for neuroimaging scanner, age, race, trauma type, and sex.

Table 2. Clinical and demographic information of the conceptual replication cohort.

	Month 1 Timepoint	Month 6 Timepoint
	$N = 65$	$N = 33$
Sex, female/male	22/43	9/24
Age, mean (SD)	35.7 (12.9)	36.4 (13.4)
Scanner (%)		
1	19 (29%)	6 (18.2%)
2	10 (15%)	1 (3%)
3	36 (55%)	26 (78.8%)
Race/Ethnicity (%)		
Non-Hispanic Black	47 (72.3%)	24 (72.7%)
Non-Hispanic White	11 (16.9%)	6 (18.2%)
Hispanic	4 (6.2%)	2 (6.1%)
Non-Hispanic other	3 (4.6%)	1 (3%)
Education		
Doctoral degree	1 (1.5%)	1 (3%)
Master's degree	3 (4.6%)	2 (5.9%)
Some graduate school	1 (1.5%)	1 (3%)
Bachelor's degree	7 (10.7%)	3 (9.1%)
Associate's/some college	26 (40%)	12 (36.4%)
High school degree or below	27 (41.5%)	14 (42.4%)
Trauma type (%)		
Motor vehicle collision	54 (83%)	25 (78.8%)
Physical assault	4 (6.2%)	3 (9.1%)
Other	7 (10.8%)	5 (15.2%)
1-month PSS, mean (SD)	15.4 (11.8)	15.6 (11.6)
6-month PSS, mean (SD)	8.8 (9.3)	8.8 (9.1)

PTSD Symptom Scale (PSS) Range: 0–51.

Sensitivity and exploratory analyses. Follow-up sensitivity analyses with pre-trauma (Discovery cohort)/peri-trauma (Replication cohort) PTSD symptom scores and childhood trauma (CTQ) scores were then conducted. See *Supplementary Materials* for DES-B analyses and sensitivity analysis details. We additionally tested for BLA reactivity to fearful or neutral faces separately: within the left and right BLA ROIs, contrasts were extracted for the main effect of fearful faces>implicit baseline, and neutral faces>implicit baseline, and models were run with this main effect term as the primary predictor. To explore associations with regions outside the BLA, we performed whole-brain multiple regression analyses and supplemental central amygdala ROI analyses (reported in *Supplementary Methods and Results)*.

Discovery cohort functional connectivity (FC) analyses. Finally, to explore any change in the functional connectivity (FC) of the BLA over the months following trauma, seed-to-voxel FC analyses were conducted using the left BLA as a seed region, based on the strongest association between response to threat and PTSD symptoms (See *Supplementary Materials* for analysis details).

RESULTS

Neural responses to social threat cues

Whole brain analysis of task-related activation revealed greater responses to fearful>neutral faces in the right amygdala, right hippocampus, right middle temporal gyrus, left middle occipital gyrus, and the left inferior orbitofrontal gyrus at 2-weeks post-trauma, $p_{FWE} < 0.05$ (Fig. 1A).

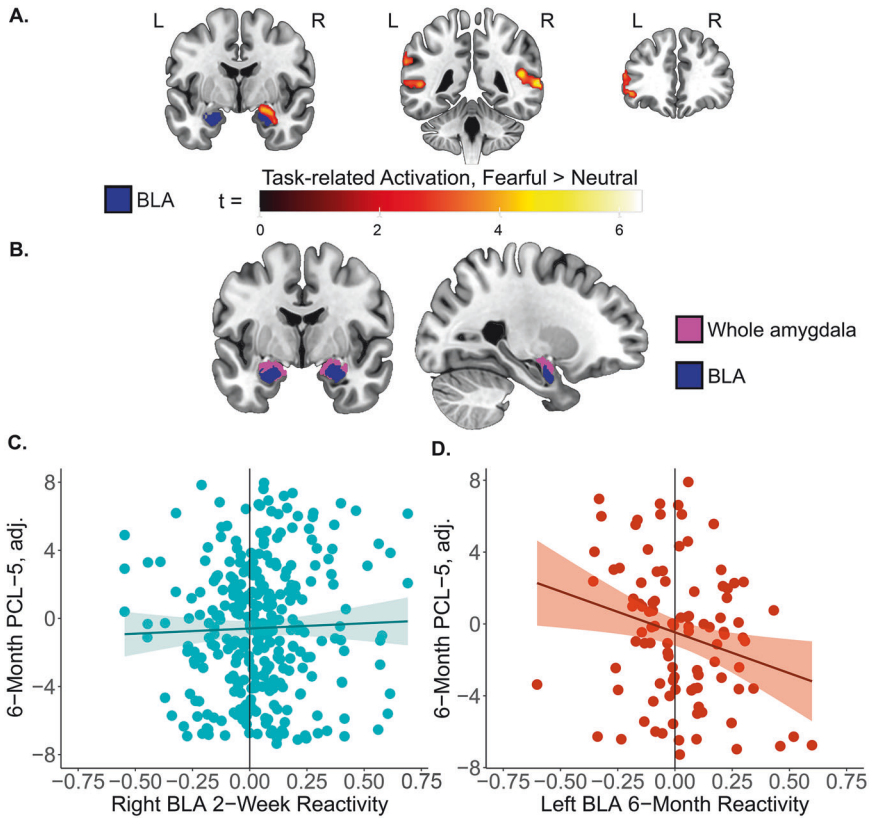

Fig. 1 Task-related whole-brain activation and significant associations between the BLA response to social threat cues and PTSD symptom severity in the Discovery cohort. Whole brain analyses of task-related activation revealed greater response to fearful > neutral faces in the right amygdala ($z = 6.27$, x,y,z = 30,-6,-18, $k = 230$), right middle temporal gyrus ($z = 5.47$, x,y,z = 66,-44,8), left middle occipital gyrus ($z = 4.35$, x,y,z = −54,-74,14, $k = 804$), and the left inferior orbitofrontal gyrus ($z = 4.05$, x,y,z = −46,36,-6, $k = 292$) at 2-weeks post-trauma, $p_{FWE} < 0.05$. Segmentation of the BLA (blue) is shown to demonstrate overlap (**A**). Segmentation of the BLA (blue) is shown in comparison to the whole amygdala (pink) (**B**). ROI analyses found right BLA reactivity to fearful>neutral faces at 2-weeks significantly and positively correlates with 6-month PCL-5 scores (**C**), and left BLA reactivity to fearful>neutral faces at 6 months significantly and negatively correlates with 6-month PCL-5 scores (**D**).

Relationship between 2-week and 6-month BLA ROI reactivity and PTSD symptoms

At the 2-week neuroimaging visit, right BLA reactivity positively predicted 6-month PCL-5 (ΔPseudo-$R^2 = 0.001$, IRR = 1.19, $p = 0.004$; Table S6, Fig. 1B). This effect persisted in a model controlling for pre-trauma PTSD symptoms (IRR = 1.23, $p < 0.001$), but not childhood trauma (IRR = 0.94, $p = 0.33$; Table S7). Separate examination of the main effects for fearful and neutral faces showed no individual association for either fearful or neutral faces in predicting 6-month PCL-5 (fearful:IRR = 0.99, $p = 0.99$; neutral:IRR = 0.94, $p = 0.12$; Table S8), suggesting that only the differential response to fearful vs. neutral faces was related to risk for later high symptoms. Left BLA reactivity did not predict 6-month PCL-5 (IRR = 1.09, $p = 0.17$). Two-week BLA reactivity was not associated with 2-week PCL-5 (left:IRR = 0.96, $p = 0.43$; right:IRR = 1.13, $p = 0.01$; Table S3) when correcting for multiple comparisons.

At the 6-month neuroimaging visit, lower left BLA reactivity to threat predicted greater concurrent PTSD severity (ΔPseudo-$R^2 = 0.04$, IRR = 0.38, $p < 0.001$; Table S11, Fig. 1C). This effect persisted when covarying for pre-trauma PTSD symptoms (IRR = 0.46, $p < 0.001$; Table S12) or childhood trauma (IRR = 0.38, $p < 0.001$; Table S12). Separate examination of fearful faces and neutral faces suggested that this effect was impacted by a lower response to fearful face stimuli—the BOLD response to neutral faces did not predict PTSD severity (IRR = 1.09, $p = 0.08$; Table S13), but response to fearful faces was negatively related to PTSD severity (IRR = 0.87, $p = 0.006$; Table S13). Right BLA reactivity at 6 months did not predict 6-month PCL-5 (IRR = 0.93, $p = 0.48$; Table S11).

Longitudinal change in BLA ROI reactivity and PTSD symptoms

We then investigated how BLA ROI reactivity changed over time and its relationship with symptom recovery. There was a significant decrease in PCL-5 scores between time points ($t(98) = -3.46$, $p < 0.001$), consistent with symptom recovery. There was no significant change over time in threat reactivity within the left or right BLA, when considering all participants together irrespective of symptoms ($p > 0.05$; Fig. 2C). There was high variability across individuals, with approximately half of participants showing a numerical increase in BLA reactivity ($n = 49$) and half showing a decrease ($n = 50$), range = −1.04–0.78.

A greater decrease in both left and right BLA reactivity from 2 weeks to 6 months was associated with greater 6-month PTSD symptom severity (Left:ΔPseudo-$R^2 = 0.03$, IRR = 0.58, $p < 0.001$; Right:ΔPseudo-$R^2 = 0.01$, IRR = 0.65, $p < 0.001$; Table S15, Fig. 2A). Results persisted in the left BLA when covarying linear and non-linear effects of baseline (2-week) BLA reactivity, but not in the right BLA (Tables S16, 17). The effect also persisted when covarying for pre-trauma PTSD symptom severity (Left:IRR = 0.61, $p < 0.001$; Right:IRR = 0.64, $p < 0.001$; Table S18) or childhood trauma (Left:IRR = 0.61, $p < 0.001$; Right:IRR = 0.73, $p < 0.001$; Table S18). Analyses separating fearful and neutral faces suggested that this was impacted by a change in the response to neutral faces—change in the left BLA response to fearful faces

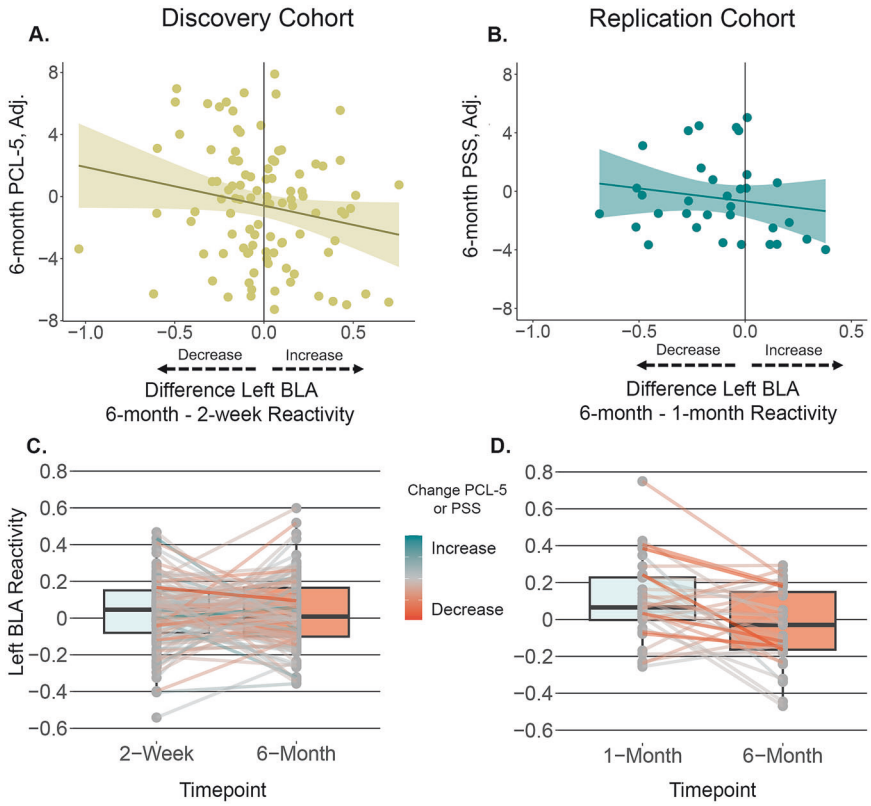

Fig. 2 Significant associations between changes in the left BLA response to social threat cues and 6-month PTSD symptom severity in both cohorts. Follow-up analyses revealed that the difference in left BLA reactivity from 2 weeks to 6 months negatively correlated with 6-month PCL-5 scores (**A**). This was replicated in the Conceptual Replication cohort, with the difference in left BLA reactivity from 1 month to 6 months negatively correlating with 6-month PSS scores (**B**). For participants with high PTSD severity at month 6, BLA fearful>neutral activity decreased. Individual left BLA reactivity change scores are displayed, with line color indicating an increase or decrease in PCL-5 scores for data set 1 (**C**) or increase or decrease in PSS score for the Conceptual Replication cohort (**D**). There was high heterogeneity in whether BLA reactivity increased or decreased over time, such that there was no group-level increase or decrease in average BLA reactivity between time points.

did not predict 6-month PTSD severity (IRR = 1.03, $p = 0.38$; Table S19, Fig. S3B). Rather, change in the response to neutral faces positively predicted 6-month PTSD severity (IRR = 1.19, $p < 0.001$; Table S19, Fig. S3A). An increase in left BLA response to neutral faces, rather than a decrease in response to fearful faces, predicted greater PTSD symptoms at 6-months post-trauma. Because individuals with both PTSD and dissociation often show a pattern of dampened emotional arousal (9), we also tested for an association of the decrease in BLA reactivity and dissociative symptoms; however, there was no association ($p > 0.05$; *Supplementary results*, Table S20).

Conceptual replication of longitudinal changes in BLA ROI reactivity predicting PTSD symptoms

We then examined if changes in BLA ROI reactivity predicting 6-month PTSD symptom severity showed generalizability in a separate cohort. The replication cohort again showed a significant decrease in PTSD symptoms from 1 month to 6 months ($t(32) = -5.81$, $p < 0.001$). In contrast with the discovery cohort, the replication cohort did show a significant decrease in BLA responsivity to threat from 1 to 6 months (Left BLA: $t(32) = 2.96$), $p = 0.006$; right BLA: ($t(32) = 2.58$ $p = 0.01$; Fig. 2D).

Importantly, the central finding from the discovery cohort was reproduced in the replication cohort, with the magnitude of the decrease in left BLA reactivity from 1 to 6 months again predicting greater 6-month PTSD symptom severity (ΔPseudo-$R^2 = 0.01$, IRR = 0.55, $p = 0.03$; Table S22, Fig. 2B). The effect persisted when covarying for peri-trauma PTSD symptoms (IRR = 0.09, $p < 0.001$; Table S23), but not childhood trauma (IRR = 0.82, $p = 0.53$; Table S23). In analyses separating fearful and neutral faces, the change in left BLA BOLD signal was negatively related to 6-month PSS scores for both fearful (IRR = 0.54, $p < 0.001$; Table S24) and neutral faces (IRR = 0.52, $p < 0.001$; Table S24).

In this cohort, the effect was reversed for the right BLA. That is, a *smaller* decrease in right BLA reactivity from 1 to 6 months was associated with 6-month PTSD symptoms (ΔPseudo-$R^2 = 0.01$, IRR = 1.63, $p = 0.03$; Table S22). This effect persisted when covarying for peri-trauma PTSD symptoms (IRR = 0.29, $p = 0.002$; Table S23), but not childhood trauma (IRR = 0.83, $p = 0.48$; Table S23). In analyses separating fearful and neutral faces, the change in right BLA reactivity to fearful faces was negatively related to 6-month PSS scores (IRR = 0.39, $p < 0.001$; Table S24), and the same was true for neutral faces (IRR = 0.38, $p < 0.001$; Table S24).

Discovery cohort functional connectivity (FC) analyses

At 6-months post-trauma, there was significant temporal coupling between the left BLA and a set of brain regions typically involved in threat processing including the left hippocampus/amygdala, right amygdala, right fusiform gyrus, right temporal pole, and right precentral gyrus (Fig. 3A). No region showed a significant longitudinal increase or decrease in FC with the left BLA, $p_{FWE} > 0.05$, when examining the whole sample irrespective of PTSD symptoms. However, the change in FC from 2 weeks to 6 months between the left BLA and a cluster overlapping with the bilateral precuneus, right superior parietal lobe, and bilateral post

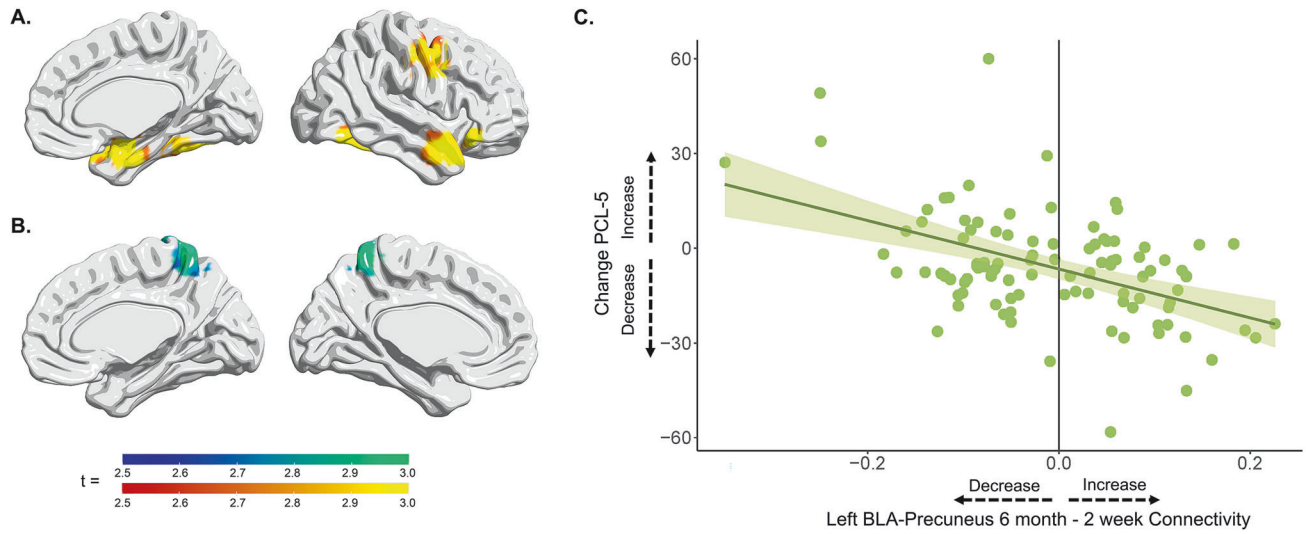

Fig. 3 Left BLA functional connectivity. A map of functional connectivity at 6 months post-trauma, with the left BLA as a seed region, is displayed for fearful faces to illustrate the set of regions showing significant temporal coupling with the BLA in the overall sample. There was significant FC between the left BLA and a set of brain regions typically involved in threat processing including the left hippocampus and amygdala (x,y,z = −24,-6,-22), right amygdala (x,y,z = 22,-4,-24), right fusiform gyrus (x,y,z = 46,-60,-22), right temporal pole (x,y,z = 42,8,-24), and right precentral gyrus (x,y,z = 42,-4,42) (**A**). A map of change in negative functional connectivity to fearful faces as negatively correlating to change in PCL-5 scores is also shown (**B**). For illustrative purposes, the functional connectivity values for fearful faces were extracted from the precuneus/post-central gyrus cluster, to show the negative correlation between change in left BLA-precuneus connectivity and change in PCL-5 scores (**C**).

central gyrus was negatively correlated with change in PTSD symptom severity (x,y,z = 16,-48,68, $p_{FWE} < 0.05$, Fig. 3), such that a decrease in FC predicted an increase in PCL-5 scores. This decrease in FC predicted a decrease in left BLA reactivity to fearful>neutral faces ($r = 0.27$, $p = 0.006$). Network overlap analysis marks this cluster as falling primarily within the dorsal attention network B (DAN; Fig. S4A, B**)**.

DISCUSSION

Amygdala hyperreactivity to threat has been reported as a hallmark of PTSD. In this large, longitudinal, multisite analysis of civilian PTSD symptoms among adults who had an acute traumatic event, we replicated the expected pattern of early post-trauma right BLA hyperreactivity as a predictor of PTSD symptoms months later [36], analyzed as an a priori region of interest. However, instead of BLA threat reactivity being a trait-like predictor, our results point to neural changes that occur in the time following an acute traumatic event, with a longitudinal decrease in BLA reactivity and lower six-month BLA reactivity associated with greater PTSD severity at six months post-trauma. This finding was also confirmed in an external replication cohort. The decrease in left BLA reactivity was also linked with a decrease in its FC with the DAN. This investigation is one of the few to assess longitudinal brain function across multiple time points in the time following acute trauma, and the only study that has assessed post-trauma changes in neural reactivity to threat cues with respect to PTSD symptoms. Together these findings provide evidence that BLA function, particularly for the left hemisphere, may be less directly coupled with PTSD symptom severity than previously thought.

Past studies examining the amygdala before or shortly after trauma support the idea that amygdala hyperreactivity predicts present and future PTSD symptom severity [18, 35, 36, 55, 56], including in a smaller subset of AURORA participants [57]. However, bilateral or left amygdala hypo-reactivity has been observed in several studies in relation to PTSD, particularly in the context of dissociation and emotional numbing symptoms [22, 58, 59] or in response to highly arousing stimuli but not moderately arousing stimuli [60, 61]. Only one study has examined longitudinal amygdala responses to threat at multiple post-trauma time points, and found that hyperactivation of the right amygdala shortly post-combat returns to pre-combat levels 1.5 years following deployment, in a small sample of $n = 14$ [37, 38], but did not investigate relationships with PTSD symptoms. In a conceptual parallel with these prior longitudinal findings, we saw a general pattern of high right BLA reactivity shortly after trauma which corresponded to later PTSD risk. However, in the left BLA, we unexpectedly observed that those individuals who demonstrated a shift over time to lower threat reactivity had higher PTSD symptoms. This shift could potentially be due to a normalization of the BLA to unknown pre-trauma levels [37, 38] following an increase of BLA reactivity early post-trauma [36, 62], a form of BLA exhaustion, such as through dysregulation of norepinephrine or glutamate systems [63–67] which are potentially influenced by childhood trauma in the Replication cohort [68–70], or a practice effect response to repetitions of the task [45]. While we do not have a measure of pre-trauma BLA reactivity, a "return to pre-trauma baseline" would imply a corresponding reduction in PTSD symptomology, which was not observed in this investigation. As we see lower left BLA reactivity predicting PTSD psychopathology and persisting after sensitivity analyses, we suspect that a form of dysregulation of threat reactivity occurs over time in those with higher symptom severity.

Although we considered the comparison of fearful vs. neutral faces in the BLA to be the primary predictor, some nuanced findings emerged when considering fearful and neutral faces separately. In the discovery cohort, an increase over time in the left BLA response to neutral faces, not fearful faces, predicted 6-month PTSD symptoms. This potentially indicates a generalization effect, in which participants with higher PTSD severity experience an increase in generalizing social threat responses to neutral stimuli [71, 72]. Interestingly, in the replication cohort, PTSD symptoms were related to decreases in both fearful and neutral face reactivity for both the left and right BLA, with lower responses to fearful faces driving change in fearful>neutral left

BLA findings, and higher responses to fearful faces driving right BLA findings. This would again suggest an exhaustion or return-to-baseline effect in the left BLA. However, we consider the results that separate fearful and neutral faces to be secondary, and exploratory, because the neutral faces act as an important control for neural responses to the perceptual components of face presentation.

Hemispheric differences are apparent in these results, with higher right BLA reactivity across timepoints and decreasing left BLA reactivity by 6-months post-trauma corresponding with PTSD symptoms. Prior studies suggest potential emotional lateralization across hemispheres, hypothesizing that the right amygdala is dominant in processing emotional stimuli, or particularly negative emotional stimuli, and emotional arousal [73, 74], while the left is dominant in processing either positive emotional stimuli or cognitive control related to emotion [74–76]. While the literature regarding lateralization is generally phenomenological, with few causal tests of differential function in the left versus right, the lateralization findings reported previously and in the current study may merit consideration for future causal tests in e.g., neuromodulation or lesion mapping studies.

Although we cannot draw causal conclusions, our FC findings suggest that changes in BLA-cortical temporal coupling impact mental health in recently trauma-exposed humans. We did not see differences in amygdala-vmPFC or -hippocampus FC predicting PTSD severity, as reported in prior studies. However, these studies only examined one time point [12, 23–25], with some in tandem reporting hyperactive amygdala results [12]. Instead, decreased left BLA reactivity in individuals with increasing PTSD symptoms was associated with decreased temporal coupling with precuneus, superior parietal, and post central gyrus regions, overlapping with the DAN. The DAN is involved in orienting spatial attention and top-down attentional control [77], and reduced or delayed recruitment of the DAN is associated with PTSD [55, 78]. Our finding is in line with prior work, which finds increases in attention network response to emotional stimuli predict PTSD symptom improvement [79]. Decreased FC between the DAN and BLA may indicate downregulation of top-down attentional allocation to the social threat stimuli. This would potentially mean that individuals with increasing PTSD severity between time points showed a decrease in orienting to social threat cues, again either due to a generalization or exhaustion effect.

We note several limitations. Due to the nature of the study, individuals were recruited only in the aftermath of an acute traumatic event. Although self-reported prior trauma was incorporated into our analyses, we do not have data on BLA reactivity to threat pre-trauma. PTSD symptom severity was measured using the PCL-5 or the PSS, both self-report measures, and not a clinical diagnostic interview. The DES-B evaluates reported dissociative experiences, not clinical dissociation, and is also a self-report measure and not a clinical diagnostic interview. The study task examined responses to social threat, not trauma-specific stimuli, in a population where many participants did not experience interpersonal trauma. The BLA, as well as other amygdala nuclei, are small regions that can be difficult to precisely resolve with current fMRI data acquisition. Aside from the central amygdala, we did not assess other amygdala nuclei due to limitations in scan resolution, and therefore do not address whether the results are specific to the BLA. There was a large decrease in participants who completed the MRI scans between timepoints in the discovery cohort, dropping from $n = 304$ to $n = 99$. This decrease was due to a randomized allocation plan that did not allocate all participants to receive a follow-up scan, as well as impacts of the COVID-19 pandemic on the ability to collect data during many participants' follow-up time windows. Finally, it is possible that findings may not generalize across populations, as our recruitment was limited to those whose trauma resulted in an ED visit, and consisted mostly of motor vehicle collisions, followed by physical assaults for both datasets. Further research is needed to test whether the findings from this investigation generalize to veterans, interpersonal trauma survivors, and other groups. However, we note that AURORA is a large, diverse, and multisite study, thus conferring strength of external validity to similar populations, with left BLA findings replicating in the single-site replication cohort.

To conclude, the findings suggest a paradigm shift in how we conceptualize and measure the role of the amygdala in PTSD. The surprising PTSD-related decline in left BLA reactivity and its FC with the DAN provide relatively strong evidence that BLA reactivity to threat in the early aftermath of trauma is not a stable phenotype that contributes to the ongoing maintenance of symptoms in individuals who end up with chronic PTSD. Instead, this study finds that changes within the amygdala in the months following acute trauma may contribute to chronic PTSD risk. Regarding treatment, a potential "flame out" of the left BLA in the first 6 months post-trauma suggests that early intervention strategies targeting amygdala-based upregulation of fear and arousal must be delivered fairly early after trauma, focusing on the right hemisphere. Regard for neural dynamics in the time following trauma should be considered in the planning of interventions that target dysregulated threat neurocircuitry.

DATA AVAILABILITY

Data and/or research tools used in the preparation of this manuscript were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier(s): NIMH Data Archive Digital Object Identifier (DOI) https://doi.org/10.15154/5t8n-fj46. Data and analysis code are available via https://github.com/aroeckner/BLA. Any additional information required to reanalyze the data reported in this paper is available from Jennifer Stevens, PhD (jennifer.stevens@emory.edu).

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ACKNOWLEDGEMENTS

The investigators wish to thank the trauma survivors participating in the AURORA Study. Their time and effort during a challenging period of their lives make our efforts to improve recovery for future trauma survivors possible.

AUTHOR CONTRIBUTIONS

SAM, RC, KJR, KCK, ARR, JSS, RH, SJHvR, TDE, NH, VPM, LAML, TJ, SLH and SEB contributed to the conceptualization, including formulation or evolution of overarching research goals and aims, of the study. FLB, XA, TCN, GDC, SDL, LTG, SLR, JJ, DAP, JFS, SEH, SAM, RCK, KJR, KCK, SJHvR, JSS, TDE, NH, VM, LL, TJ, SLH. and SB contributed to the methodology of the study, including development or design of methodology and creation of models. ARR, JSS, SJHvR, J TDE, NH, VM, LL, TJ, SLH, SB and KJR contributed to the neuroimaging data collection, formal analyses and validation of the study. SLH, FLB, XA, JSS, TCN, GDC, TJ, SDL, LTG, SLR, JPH, ABS, CL, PIMJr, PLH, SS, CWJ, BEP, RAS, JLP, MJS, CP, DAP, RCM, RMD, NKR, BJO, LDS, SAM, RCK, KJR and KCK conducted the research and investigation process, specifically, performing the experiments or data and evidence collection. SLH, FLB, XA, JSS, TCN, GDC, TJ, SDL, LTG, SLR, JPH, ABS, CL, PIMJr, PLH, SS, CWJ, BEP, RAS, JLP, MJS, CP, DAP, RCM, RMD, NKR, BJO, LDS, SAM, RCK., KJR. and KCK provided the resources for the study, including provision of study materials, patients, laboratory samples, instrumentation, computing resources or other analysis tools. SLH, FLB, XA, JSS, TCN, GDC, TJ, SDL, LTG, SLR, SAM, RCK, KJR and KCK were responsible for data curation, including management activities to annotate, scrub data and maintain research data for initial use and later reuse. ARR, ER-HL, and JSS were responsible for writing the original draft, including preparation, creation and presentation of the published work. All authors contributed to the paper by reviewing and editing the original draft. ARR and JSS were responsible for data visualization, including preparing, creating and presenting the published work, specifically, visualization and data presentation. SAM, RCK, KJR, KCK, and JSS were responsible for supervision, including oversight and leadership for the research activity planning and execution, including mentorship external to the core team. SLH, FLB, JSS, TJ, JPH, ABS, CL PIMJr, PLH, SS, CWJ, BEP, RAS, JLP, MJS, CP, RCM, RMD, NKR, NJO, LDS and SB were responsible for project administration, including management and coordination, responsibility for the research activity planning and execution. SAM, RCK, KJR and KCK were responsible for acquisition of the financial support for the project leading to this publication. ARR was responsible for funding supporting her effort on this publication.

FUNDING

This research was supported by the National Institute of Mental Health K00 MH119603, K01 MH118467, U01 MH110925, and F31 MH126623, as well as the U.S. Department of Defense W81XWH-22-C-0122. This project was supported by NIMH under U01MH110925, the US Army MRMC, One Mind, and The Mayday Fund. The content is solely responsibility of the authors and does not necessarily represent the official views of any of the funders. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDA.

COMPETING INTERESTS

Dr. Harnett reports grant support from the National Institute of Mental Health, K00 MH119603. Dr. Lebois reports unpaid membership on the Scientific Committee for the International Society for the Study of Trauma and Dissociation (ISSTD) and grant support from the National Institute of Mental Health, K01 MH118467. ISSTD and NIMH were not involved in the analysis or preparation of the manuscript. Dr. van Rooij is supported by the NIMH (K01MH121653). Dr. Neylan has received research support from NIH, VA, and Rainwater Charitable Foundation, and consulting income from Jazz Pharmaceuticals. In the last three years Dr Clifford has received research funding from the NSF, NIH and LifeBell AI, and unrestricted donations from AliveCor Inc, Amazon Research, the Center for Discovery, the Gates Foundation, Google, the Gordon and Betty Moore Foundation, MathWorks, Microsoft Research, Nextsense Inc, One Mind Foundation, the Rett Research Foundation, and Samsung Research. Dr Clifford has financial interest in AliveCor Inc and Nextsense Inc. He also is the CTO of MindChild Medical and CSO of LifeBell AI and has ownership in both companies. These relationships are unconnected to the current work. Dr. Germine receives funding from the National Institute of Mental Health (R01 MH121617) and am on the board of the Many Brains Project. My family also has equity in Intelerad Medical Systems, Inc. Dr Rauch reported serving as secretary of the Society of Biological Psychiatry; serving as a board member of Community Psychiatry and Mindpath Health; serving as a board member of National Association of Behavioral Healthcare; serving as secretary and a board member for the Anxiety and Depression Association of America; serving as a board member of the National Network of Depression Centers; receiving royalties from Oxford University Press, American Psychiatric Publishing Inc, and Springer Publishing; and receiving personal fees from the Society of Biological Psychiatry, Community Psychiatry and Mindpath Health, and National Association of Behavioral Healthcare outside the submitted work. Dr. Sheikh has received funding from the Florida Medical Malpractice Joint Underwriter's Association Dr. Alvin E. Smith Safety of Healthcare Services Grant; Allergan Foundation; the NIH/NIA-funded Jacksonville Aging Studies Center (JAX-ASCENT; R33AG05654); and the Substance Abuse and Mental Health Services Administration (1H79TI083101-01); and the Florida Blue Foundation. Dr. Jones has no competing interests related to this work, though he has been an investigator on studies funded by AstraZeneca, Vapotherm, Abbott, and Ophirex. Dr. Datner serves as Medical Advisor and on the Board of Directors for Cayaba Care. Dr. Joormann receives consulting payments from Janssen Pharmaceuticals. Dr. Harte has no competing interest related to this work, though in the last three years he has received research funding from Aptinyx and Arbor Medical Innovations, and consulting payments from Aptinyx. Dr. Koenen's research has been supported by the Robert Wood Johnson Foundation, the Kaiser Family Foundation, the Harvard Center on the Developing Child, Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, the National Institutes of Health, One Mind, the Anonymous Foundation, and Cohen Veterans Bioscience. She has been a paid consultant for Baker Hostetler, Discovery Vitality, and the Department of Justice. She has been a paid external reviewer for the Chan Zuckerberg Foundation, the University of Cape Town, and Capita Ireland. She has had paid speaking engagements in the last three years with the American Psychological Association, European Central Bank. Sigmund Freud University – Milan, Cambridge Health

Alliance, and Coverys. She receives royalties from Guilford Press and Oxford University Press. In the past 3 years, Dr. Kessler was a consultant for Cambridge Health Alliance, Canandaigua VA Medical Center, Holmusk, Partners Healthcare, Inc., RallyPoint Networks, Inc., and Sage Therapeutics. He has stock options in Cerebral Inc., Mirah, PYM, and Roga Sciences. Dr. McLean served as a consultant for Walter Reed Army Institute for Research and for Arbor Medical Innovations, and BioXcel Therapeutics, Inc. Dr. Ressler has performed scientific consultation for Bioxcel, Bionomics, Acer, and Jazz Pharma; serves on Scientific Advisory Boards for Sage, Boehringer Ingelheim, Senseye, and the Brain Research Foundation, and he has received sponsored research support from Alto Neuroscience. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41386-025-02115-1.

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