Sequential Fear Generalization and Network Connectivity in Trauma Exposed Humans With and Without Psychopathology

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Abstract

While impaired fear generalization is known to underlie a wide range of psychopathology, the extent to which exposure to trauma by itself is resulted in deficient fear generalization and its neural abnormalities is yet to be studied. Similarly, the neural function of intact fear generalization in people who endured trauma and did not develop significant psychopathology is yet to be characterized. Here, we utilized fMRI, a generalization task, and a network connectivity approach to clarify behavioral and neural markers of trauma and resilience. The generalization task enabled longitudinal assessments of threat discrimination learning. Trauma-exposed (TEs) participants, compared to healthy controls (HCs) showed lower activity reduction in salience network (SN) and right executive control network (RECN) across the two sequential generalization stages, and worse discrimination learning in SN measured by linear deviation scores (LDS). Comparison of resilient, trauma-exposed healthy participants (TEHCs), trauma exposed individuals presenting with psychopathology (TEPGs), and HCs, revealed a resilience signature of network connectivity differences in the RECN during generalization learning measured by LDS. These findings may indicate a trauma exposure phenotype that has the potential to advance the development of innovative treatments by targeting and engaging specific neural dysfunction among trauma-exposed individuals, across different psychopathologies.

Significance Statement

Exposure to trauma is highly prevalent and its mental health consequences are frequently debilitating. While most exposed individuals will exhibit resilience and not develop significant psychopathology, a significant number of people will develop long-term psychiatric illness. The present study aimed to identify unique behavioral and neural markers of trauma and resilience, by utilizing fMRI and a generalization/discrimination task. Findings suggest that trauma signature may involve enhanced threat detection and monitoring network engagement via the salience network (SN), whereas resilience signature engages the right executive network (RECN), which may serve as a compensatory mechanism. Findings have the potential to advance novel treatment development by targeting neural dysfunction among trauma-exposed individuals, across different psychopathologies.

Introduction

More than one third of people exposed to traumatic events, such as wars, disasters, and assaults, are likely to develop significant psychopathology, including posttraumatic stress disorder (PTSD), panic disorder (PD), generalized anxiety disorder (GAD), and major depression disorder (MDD) (1-4). As symptoms of these disorders frequently overlap (5), their biological underpinnings are often shared (6, 7). Addressing the question of whether trauma exposure is associated with a distinct neural signature across psychopathologies may advance our understanding of the corresponding neural dysfunction. Yet, efforts to advance knowledge regarding trauma-related neural aberrations have been hampered by adhering to traditional diagnostic systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (8), neglecting more objective markers including those clarified by brain imaging (9). Furthermore, extant

research examining neural biomarkers of trauma exposure has focused almost solely on patients with PTSD, limiting our understanding of potential shared mechanisms across psychopathologies. This focus on PTSD has also complicated efforts to clarify whether resilience (i.e., exposure to trauma without developing significant psychiatric symptoms) may have a unique neural signature, with research on resilience being relatively sparse (10-12). In an effort to address these gaps in knowledge, the present study aimed to clarify the behavioral and network functional magnetic resonance imaging (fMRI) markers of trauma and resilience in trauma-exposed people with and without psychopathology, and among people who were never exposed to trauma.

Previous studies have implicated excessive threat generalization (termed also threat or conditioned overgeneralization) as a potential endophenotype of several psychopathologies, including PTSD, PD, and GAD (13, 14). Threat generalization and discrimination are essential for learning about future threats. Generalization transfers a conditioned response from one stimulus to another similar, yet different, stimulus (15). In threat-related fear responses, individuals who overgeneralize transfer fear from a dangerous stimulus to a less dangerous or even safe one, reflecting excessive fear and resulting in threat discrimination difficulties (15). A recent meta-analysis study has shown significantly heightened behavioral fear generalization across anxiety-related disorder participants including GAD, PTSD, PD, SAD than controls, however, this study was limited to behavioral and psychophysiological data only (16).

Threat generalization and discrimination have been shown to be processed via two distinct computations. The first, *pattern separation*, takes similar neural activity patterns and converts them to distinct neural representations. The second, *pattern completion*, operates on these distinct representations and either ignores the difference, if negligible, or generates orthogonal neural representations if the difference is sufficiently large (17). Several brain areas are involved in these distinct computational process and are responsible for threat generalization and discrimination. These include the hippocampus (18, 19), ventral prefrontal cortex (vPFC) (1, 13), insula (20), dorsomedial prefrontal cortex (dmPFC) (21), anterior cingulate cortex (ACC), and thalamus (20). Deficits in these brain areas, related to generalization/discrimination, have been attributed to PTSD (22, 23). The involvement of these neural areas also underscores the potential role of several essential brain networks in generalization/discrimination, including the default mode network (DMN), salience network (SN), and executive control network (ECN). These brain networks were also shown to play a key role in memory (DMN) (24), bottom-up (SN) and top-down executive control processes (ECN) (25).

Understanding the ways by which trauma exposure may alter these brain networks, and where they diverge from those of resilient individuals, is essential for clarifying the underlying basis of human psychopathology in the aftermath of trauma. To thoroughly elucidate behavioral and neural markers of trauma exposure and resilience, we utilized a generalization/discrimination task previously tested in patients with PD (14), GAD (26) and PTSD (22). These studies show that psychiatric patients, compared to normal controls, exhibit stronger generalization, implicating it as a putative marker of disrupted threat discrimination (13-15, 24, 26-28). However, no study to date has assessed this neural marker among people exposed to trauma across psychiatric illnesses or among resilient participants who were exposed

to trauma, but did not develop any significant psychiatric symptoms. In addition, no study to date has looked at how trauma exposed individuals learn to discriminate between cues over time. Learning to discriminate is an essential computational process whereby exposure to cues creates either different neural representations for each cue. Understanding how these representations are built over time can give us an insight into how psychopathology develops and is maintained and how resilient counterparts overcome it. Hence, the task used here entails two consequent generalization stages, termed early and late generalization (EG, LG), enabling to delineate the sequential trajectory of threat discrimination learning over these two stages. One study compared the trial-by-trial course of risk rating during generalization phase between PTSD and subthreshold PTSD to trauma-exposed controls (29). This study provided initial evidence that relative to trauma-exposed controls, those with PTSD and subthreshold PTSD displayed significantly elevated generalization in early but not late trials (29). However, research has yet to characterize the temporal associations between threat discrimination and network activation over the course of two consecutive generalization phases.

In the present study, aiming to characterize the markers of threat generalization /discrimination of trauma exposure and resilience, we assessed both the behavioral risk rating and network connectivity of threat discrimination, which has been largely unexplored in trauma-exposed populations. Specifically, behavioral risk rating and related network connectivity of the DMN, SN, and ECN were assessed. To clarify the behavioral and neural markers of trauma, trauma-exposed participants (TE) and healthy controls (HC) were compared. To identify the behavioral and neural signature of resilience, trauma-exposed participants with psychopathology (TEPG) were compared to trauma-exposed healthy controls (TEHC) and healthy controls (HC) with no trauma exposure.

Methods

Participants

One hundred fourteen participants (79 TEs and 35 HCs) completed the study protocol (see Table 1 and Figure S4). Of the 79 TE participants, 41 had psychopathology at the level of a psychiatric diagnosis (TEPG), and 38 were trauma-exposed healthy controls with no diagnosis (TEHC; see Table 1 and Figure S4). Participants were recruited by local advertisements, websites, and word-of-mouth referrals and evaluated at the New York State Psychiatric Institute (NYSPI). The methods were performed in accordance with relevant guidelines and regulations and approved by NYSPI IRB. All participants provided written consent to take part in the study.

Behavioral ratings

This task consists of six types of stimuli including conditioned stimuli (CSs including CS+: danger cue; oCS-: o shape safe cue; vCS-: v shape safe cue) and three generalization stimuli (GSs including GS1, GS2, GS3). There were a string of colored crosshairs (blue, yellow, red, green, and purple) presented serially for a duration of 800 ms each, in a quasi-random order in the center of the viewing screen during 4 s presentation of each stimulus. The inter-trial interval (ITI) periods last 2.4 s (three crosshairs) or 4.8 s

(four crosshairs). Participants were instructed to continuously monitor the stream of colored crosshairs and rate their perceived level of risk for shock as quickly as possible following each red cross using a three-button fiber optic response pad (Lumina LP-404 by Cedrus), where 0='no risk', 1='moderate risk' and 2='high risk'. Risk ratings were recorded with Presentation software (Neurobehavioral Systems). For half of CS/GS trials, one of five crosshairs was red, and the remaining trials included no red crosshairs. Additionally, on reinforced CS+ trials, the red crosshair never appeared in the fourth or fifth position to avoid interference from shock on behavioral responses. Finally, self-reported anxiety to CS+, oCS-, and vCS- were retrospectively assessed following the pre-acquisition, acquisition, and generalization phases using a 10-point scale. The behavioral risk rating analysis excluded non-learner participants, indicated by rating the vCS- higher than CS+ during task-related risk rating or the post-task questionnaire (28).

Design

The generalization paradigm included three phases (Figure S5): (i) pre-acquisition-consisting of 20 trials of each stimulus type (CS+, GS1, GS2, GS3, oCS- and vCS-), all presented in the absence of any shock US; (ii) acquisition-including 15 CS+, 15 oCS-, and 15 vCS-, with 12 of 15 CS+ co-terminating with shock (80% reinforcement schedule) and (iii) generalization-including an early generalization (EG) stage and late generalization (LG) stage, each comprised of 10 trials of each stimulus type (unreinforced CS+, GS1, GS2, GS3, oCS-, vCS-) and an additional 5 CS+ co-terminating with shock (33% reinforcement schedule) to prevent extinction of the conditioned response while leaving 10 unreinforced CS+ to index responses uninfluenced by the shock US. Trials of all three phases were arranged in quasi-random order such that no more than two stimulus-type of the same class occurred consecutively. An additional constraint for the generalization phase was the arrangement of trials into six blocks of 13 trials each (i.e., two unreinforced CS+, one reinforced CS+, two oCS-, two vCS-, two GS1, two GS2, two GS3) to ensure an even distribution of trial types throughout runs.

Image Acquisition and analysis

Seventy-seven participants were scanned using a 3T General Electric MR750, and 37 participants were scanned using a 3T General Electric PREMIER (GE Medical Systems, Waukesha, WI, USA) equipped with a 32-channel receive-only head coil. For each participant a high-resolution T1-weighted 3D BRAVO sequence was acquired using the following parameter: T1=450 mm, Flip angle =12°, field of view =25.6 cm, 256×256 matrix, slice thickness =1 mm. T2*-weighted echo-planar images (EPIs) depicting the blood-oxygen-level-dependent (BOLD) were acquired for each participant with TR=1.3 sec, TE=28 msec, FA =60°, FOV =19.2 cm, number of slices=27, slice thickness=4 mm. A head cushion was used to limit head motion.

fMRI Network Analysis

Group independent components analysis was performed using the GIFT toolbox (v3.0b, http://icatb.sourceforge.net), implemented as a MATLAB toolbox (Matlab 2020b, MathWorks Inc., Sherborn, MA, USA), to obtain functional networks that underlie fMRI data. The group spatial ICA is first

performed on all participants at once, providing an independent component spatial map and a single associated ICA time course for every component, participant, and stage. Individual participants' spatial maps and associated time courses corresponding to the group ICA maps were calculated, and significant between-group differences in the activity of the SN, ECN, and DMN networks during generalization were determined by a second-level analysis of the ICA results. To identify the components most involved in each trial type, a GLM analysis was performed. We examined the role of each ICN for each condition (CS-, GS, CS+ etc.) and how this differed according to trial type. These conditions were modeled using a GLM with the canonical hemodynamic response function (HRF) in SPM12 to examine the association between component time courses and different trial types. The resulting β-weights, a measure of each component's trial-specific amplitude, were entered into statistical analysis to identify those components significantly more engaged in each condition.

Statistical Analysis

All statistical analysis was carried out in SPSS. Levels of conditioning were assessed with paired sample t-tests comparing behavioral risk ratings to CS+ vs. oCS-, and CS+ vs. vCS- in HC and TE separately during pre-acquisition, acquisition and generalization phases. The significance threshold for these behavioral analyses were set at $p<.0167$ to adjust for multiple comparisons using Bonferroni correction (corrected for 3 comparisons).

To examine the generalization phases over time (EG, LG), for both behavior and neural markers, we first assessed changes (delta) in behavioral and neural markers over the two stages (EG-LG) for trauma exposure by comparing TE and HC using a group (TE and HC) by stimulus-type (vCS-, oCS-, GS1, GS2, GS3 and unreinforced CS+) repeated measures ANOVAs, and then assessed the changes of behavior and neural markers over the two stages (EG-LG) of resilience by further comparing TEHC and TEPG with HC using a group (TEPG, TEHC, HC) by stimulus-type (vCS-, oCS-, GS1, GS2, GS3 and unreinforced CS+) repeated measures ANOVAs.

Next, we assessed the changes in steepness of the generalization gradients across early and late stages (i.e., changes/ delta of generalization magnitudes: EG-LG) measured by linear deviation scores (LDS) (26). LDS reflect the degree to which participant level gradients depart from linearity: LDS = ([CS+, CS-] /2) - [GS1, GS2, GS3] /3)), where [CS+, CS-] /2 reflects the theoretical, linear midpoint of the gradient, and [GS1, GS2, GS3] /3 the average response to GSs. This equation provides a single number index reflecting the steepness of generalization gradients, with larger values indicating stronger generalization. We then assessed the behavioral and neural markers of trauma exposure by measuring the delta of LDS across two stages using one-way ANOVA, and then assessed the behavioral and neural markers of resilience by further comparing TEPG and TEHC with HC using one-way ANOVA. Effects of covariate corresponding to different scanners, age and sex was used in all analysis as a covariate of no interest.

For assessing the neural markers of trauma exposure and resilience, the five intrinsic connectivity networks (ICN) meeting selection criteria were used (Table S1). These networks included the salience network (SN), left executive control network (LECN), right executive control network (RECN), anterior

default mode network (a-DMN) and posterior default mode network (p-DMN). All neural imaging results were corrected for multiple comparison at p<0.01 (5 networks).

Results

Demographics and clinical characteristics of the participants

Demographic and clinical characteristics, including diagnoses, are presented in Table1. As expected, compared to HCs, TE participants had significantly higher PTSD symptoms (30), depression symptoms (31), SAD symptoms (32), panic disorder symptoms (33), GAD symptoms (34), and functional impairment (35). In addition, TEPG participants, compared with TEHCs, had higher psychopathology symptoms on all measures (all *p's*<0.001; See Table 1).

Table 1

Demographic information of the sample

		HC	TE	TEPG	TEHC
N		33	77	40	37
Sex, N (%)	Male	15 (45.5)	47 (61.0)	26	21
	Female	18 (54.6)	30 (39.0)	14	16
Race, N (%)	Black/African American	16 (48.48)	38 (49.4)	17 (42.50)	21 (56.76)
	White/Caucasian	12 (36.36)	18 (23.4)	11 (27.50)	7 (18.92)
	Asian	1 (3.04)	6 (7.8)	3 (7.50)	4 (10.81)
	Others	4 (12.12)	15 (19.5)	9 (22.50)	5 (13.51)
Age, mean years (SD)		35.09 (11.6)	36.8 (12.4)	35.75 (12.85)	37.95 (12.06)
Education, mean (SD)		15.7 (2.7)	14.7 (2.5)	14.64 (2.85)	14.71 (2.15)
CAPS, mean (SD)		-	18.8 (16.6)	31.8 (11.9)	4.7 (5.9)
HAM-D, mean (SD)		0.4 (0.8)	7.5 (7.5)	12.6 (7.0)	2.1 (2.5)
LSAS, mean (SD)		10.3 (12.7)	41.3 (34.8)	59.6 (32.4)	20.9 (24.9)
PDSS, mean (SD)		0.4 (1.6)	5.2 (6.1)	8.7 (6.2)	1.3 (2.8)
SF36, mean (SD)		88.2 (7.7)	65.1 (23.7)	50.4 (19.4)	81.3 (16.3)
GAD-7, mean (SD)		0.9 (2.2)	6.4 (6.2)	10.12 (5.6)	2.2 (3.5)
Current	PTSD	0	31 (40.3)		
	MDD	0	11 (14.3)		
	PDD	0	11 (14.3)		
	GAD	0	3 (3.9)		
	SAD	0	6 (7.8)		
	PD	0	6 (7.8)		
	OCD	0	1 (1.3)		
	Substance abuse	0	0 (0.0)		
	ADHD	0	4 (5.2)		
	Insomnia	0	1 (1.3)		
	Subthreshold PTSD	0	4 (5.2)		
	Subthreshold MDD	0	3 (3.9)		

Abbreviation: CAPS: Clinician-Administered PTSD Scale-5; HAM-D: Hamilton Depression Scale; LSAS: Liebowitz Social Anxiety Scale; PDSS: Panic Disorder Severity Scale; PTSD: Posttraumatic Stress Disorder; MDD: Major Depression Disorder; PDD: Persistent Depressive Disorder; GAD: Generalized Anxiety Disorder; SAD: Social Anxiety Disorder; PD: Panic Disorder; OCD: Obsessive-Compulsive Disorder; ADHD: Attention Deficit Hyperactivity Disorder; HC: Healthy Control; TE: Trauma Exposed; TEPG: Trauma Exposed Psychopathology Group; TEHC: Trauma Exposed Healthy Control.

Behavioral risk rating (conditioning):

First, we examined the appraisal of shock risk (risk ratings to CS+ vs. vCS- or CS+ vs. oCS-) in TEs and HCs separately, across the three phases (pre-acquisition, acquisition, and generalization), using paired sample t-tests. Results showed no CS+ vs. vCS- or CS+ vs. oCS- differences at the pre-acquisition phase ($p>0.05$) in both groups. Conversely, a significant difference between the cues at acquisition ($p<0.001$) and both generalization phases ($p<0.001$) emerged in both groups (Figure S1). These results suggest that both groups learned the CS contingencies.

Threat overgeneralization/discrimination over time:

Trauma exposure markers

Behavioral markers changes of stages: To examine the behavioral differences over the two generalization phases (EG, LG), we first assessed the changes of behavioral risk rating over the two stages (delta: EG-LG) of trauma exposure by comparing TE and HC using a group (TE and HC) by stimulus-type (vCS-, oCS-, GS1, GS2, GS3 and unreinforced CS+) repeated measures ANOVAs. Results indicated no significant findings of the changes of behavioral risk rating over the two stages ($p>0.05$; Figure 1).

Next, we assessed the changes of LDS across two stages using one-way ANOVA. Results indicated no significant findings ($p>0.05$).

Neural markers changes of stages: To examine neural activity changes (delta: EG-LG) over the two generalization phases, we performed a group (TE, HC) by stimuli-type two-way ANOVA. No significant group by stimuli interaction was found. Only a corrected significant *main effect of group* emerged in SN and RECN (SN: $F=7.01$, $p=0.008$; RECN: $F=10.25$, $p=0.001$). This main effect of group was driven by HC displaying a higher reduction of SN and RECN activity, compared to TE who displayed consistently higher SN and RECN activity, over the two generalization phases (Figure 2). Other networks indicated no significant findings.

Next, we accessed the changes of LDS across two stages in each of these ICNs using one-way ANOVA. Results indicated a significant *group difference* in SN LDS ($F=7.492$, $p=0.04$ Bonferroni corrected). This was driven by higher LDS reduction in HC compared to TE ($p=0.04$ Bonferroni corrected; Figure 3).

Taken together, these analyses suggest that both groups were able to differentiate between the CS+ and the CS-, and rated the other generalization stimulus-type comparably during the task. However, compared to the TE, HC displayed a higher reduction of SN and RECN activity over the generalization stages, indicating a better learning effects. Additionally, compared with TE, HC displayed better discrimination learning over the two stages across different stimuli measured by LDS in SN. These findings suggest that while trauma exposure maintains high SN and RECN activity over time, it reduces the ability to use the SN to discriminate between the stimuli, as per the LDS.

Resilience markers

Behavioral markers changes of stages: To examine the behavioral differences over the two generalization phases (EG, LG), we first assessed the changes of behavioral risk rating over the two stages (EG-LG) of resilience by comparing TEHC, TEPG and HC using a group (TEHC, TEPG and HC) by stimulus-type (vCS-, oCS-, GS1, GS2, GS3 and unreinforced CS+) repeated measures ANOVAs. Results indicated no significant group by stimuli interaction of the changes of behavioral risk rating over the two stages (EG-LG; $p>0.05$). A significant main effects group was found ($F=6.69$, $p=0.001$), where TEPG, compared to the other two groups, showed consistently higher risk ratings across the two stages (TEPG vs. HC: $p=0.045$; TEPG vs. TEHC: $p=0.005$ Bonferroni corrected; Figure 1).

Next, we assessed the changes of LDS using one-way ANOVA. Results indicated no significant changes of LDS, indicating no group discrimination learning differences during the generalization phase.

Neural markers changes of stages: To examine neural activity changes (delta: EG-LG) over the two generalization phases, we performed a group (TEPG, TEHC, HC) by stimuli-type two-way ANOVA. No significant group by stimuli interaction was found ($p>0.05$). Only a corrected significant *main effect of group* emerged in SN and RECN (SN: $F=7.13$, $p=0.005$; RECN: $F=12.74$, $p=0.00002$ Bonferroni corrected). This main effect of group was driven by TEHC maintain higher SN and RECN activity, compared to TEPG (SN $p=0.035$ Bonferroni corrected; RECN $p=0.0006$ Bonferroni corrected) and HC (SN $p=0.001$ Bonferroni corrected; RECN $p=0.000015$ Bonferroni corrected) who displayed higher reduction of SN and RECN activity, over the two generalization phases (Figure 2). Other networks indicated no significant findings.

Next, we accessed the changes of LDS across two stages in each of these ICNs using one-way ANOVA. Results indicated a trending group difference in SN LDS ($F=3.70$, $p=0.029$) and RECN LDS ($F=4.04$, $p=0.021$). These results were driven by higher SN LDS reduction in HC group compared to the other two groups (HC vs.TEHC: $p=0.018$, HC vs.TEPG: $p=0.021$) and lower RECN LDS reduction in TEPG group compared to the other two groups (TEPG vs.HC: $p=0.029$, TEPG vs. TEHC: $p=0.01$; Figure 3).

Taken together, these analyses suggest that while all groups could differentiate between the CS+ and CS-, TEPG, compared to TEHC and HC, had higher risk ratings particularly during the LG stage. Resilience findings could be explained by maintaining high SN and RECN activity over the two stages in the TEHC, compared to the TEPG and HC. Interestingly, higher LDS reduction of SN was found in the HC, compared to TEPG and TEHCs, while higher LDS reduction was found in RECN in both the HC and TEHC groups,

compared to TEPGs. That is, while TEHC had maintained higher SN and RECN activity over time, the results show higher LDS in the RECN, suggesting a compensatory input used for discrimination. Overall, these results suggest that while trauma-exposed resilient individuals show a higher SN activity, a refined engagement of the RECN could potentially enhance their ability to successfully discriminate between stimulus-type resembling the one predicting threat.

Discussion

To examine whether exposure to trauma is associated with measurable behavioral and neural markers this study utilized an fMRI generalization/discrimination task among trauma-exposed adults with and without psychopathology, as well as healthy non trauma-exposed controls. This study is the first to assess both behavioral and neural network markers of longitudinal threat overgeneralization and discrimination. Group differences between TEs and HCs revealed a distinct signature of trauma exposure. TEs, compared to HC, showed lower activity reduction in SN and RECN across two stage, and worse discrimination learning in SN measured by LDS. Additionally, group differences between TEPGs, TEHCs, and HCs further revealed a resilience signature of network connectivity differences in the RECN during generalization learning. Overall, trauma-exposed resilient individuals demonstrated better discrimination learning over time in the RECN, compared with those who developed psychopathology. These findings may suggest a trauma exposure phenotype that has the potential to significantly advance novel treatment development by targeting specific well-delineated neural dysfunction among trauma-exposed individuals, across different psychopathologies.

Behavior signature of generalization

When exploring the temporal sequence of generalization, HC and TEHC participants showed a good discrimination between GS and CS+, while TEPGs exhibited higher risk ratings between GS3 and CS+ during generalization. Our behavior results suggest that the TEs showed overall higher risk ratings than HC. These results were driven by lower risk rating in TEHCs and HCs, compared to TEPGs, further supporting a potential resilience signature. The results support the premise that TEPGs have a harder time discriminating between cues (overgeneralizing cues) particularly as they resemble the CS+. In turn, resilient trauma-exposed counterparts where able to discriminate between the cues comparably to HCs. Indeed, our findings support previously reported discrimination deficits in PTSD (22) and anxiety (26), where PTSD groups show increased generalization to stimuli resembling the CS+. These results suggest that trauma exposure by itself does not necessarily hampers once ability to discriminate between cues, unless one develops psychopathology following exposure to trauma.

Network-based neural markers of generalization

Studying averaged generalization across the two stages in TE participants showed maintained higher overall activity in the SN, indicating a general trauma exposure marker. The SN plays an important role in graded levels of threat-related salience detection (36, 37), with usually highest levels to CS+ which gradually diminishes with decreasing CS+ resemblance. In this case, results show that HC have a higher

reduction in SN activity over time, not evident in TE participants. Additionally, the HC group had higher LDS in the SN when compared to the TE group, further indicating a trauma exposure signature. Specifically, within the HC group, the identified neural signature of overgeneralization measured by steepness of gradients (LDS) was improved over time, suggesting better discrimination in the late generalization stage, compared with the earlier one. The SN in the TE group had less of a generalization gradient and remained the same over time, suggesting poor discrimination learning in this group. Interestingly, when TE participants were further divided into TEPGs and TEHCs, we found that this SN effect was driven by the TEHC group as compared to the other two groups (TEPG; HC). This is further supported by the SN LDS analysis, which revealed that in TEHCs, like in TEPGs, there was a low correlation with discrimination during the LG stage. Overall, these results suggest that while HC are able to use the SN to improve the detection and discrimination of threat, trauma-exposed individuals cannot.

Examining the ECN, we found that TEs showed maintained RECN activity from EG to LG. However in TEHC, like in HC, RECN was associated with increased discrimination learning (LDS). Generalization effects in the ECN may represent graded decreases in cognitive load that are proportional to decreases in fear reactivity as stimulus-type differentiate from CS+. According to attentional control theory, cognitive correlates of anxiety, including worry, attentional bias toward threat, and top-down efforts to manage anxiety, consume limited working-memory resources(38). Our TEHC group findings, that the RECN activity correlation with LDS increased over time, suggest that less cognitive control network is needed as anxiety reduces over time. That is, trauma-exposed resilient individuals might rely on a refined detection and monitoring system to discriminate between stimulus-type, reducing their cognitive load, and therefore reducing their anxiety. The opposite is seen in the TEPG group, which showed high SN and RECN activity and low discrimination learning associated with these networks. This may further suggests that the ECN is needed in order to regulate anxiety and fear to discriminate those stimulus-type which more resemble the CS-.

Several limitations of the present study should be noted. First, while we were expecting to find limbic area differences, particularly in the hippocampus, this was not the case. It could be that as the present task did not involve context, there was a lack of modulatory response by the hippocampus (39). Future studies could emphasize context learning and discrimination following trauma exposure to test this hypothesis. Second, the data was collected in two scanners, and while we ensured that data was properly harmonized and controlled for scanner across all analysis, we cannot exclude the possibility that noise might be introduced when combining the two datasets. Finally, we excluded patients with psychosis, schizophrenia, and bipolar illness for which there is some evidence for trauma history, which may limit the generalizability of obtained results. Future research may consider using more lenient inclusion/exclusion criteria by expanding the range of included disorders.

In summary, our study shows evidence for both a trauma exposure signature and a resilience signature, not limited to specific psychiatric psychopathologies. The plasticity of threat and memory networks identified here may present significant opportunities for developing interventions aiming to target trauma exposure-related neural abnormalities. The SN and ECN activity emerged as key circuits of threat

generalization following trauma exposure. However, higher activity in the SN in concert with higher RECN correlation to discrimination learning may represent a resilience signature in healthy trauma-exposed individuals, who do not develop psychiatric disorders following a traumatic experience. Interventions directed at neurogenesis of the SN and ECN circuits might help increase discrimination in those who developed psychiatric disorders. Emerging research suggests that brain stimulation, particularly transcranial direct current stimulation (tDCS), a non-invasive technique, is a promising treatment for fear-related abnormalities by modulating threat memories and enhancing cognitive control via application to the prefrontal cortex. (40) Interventions, such as tDCS, of the SN and ECN may have relevance in reducing long term effects of trauma exposure and the development of post-trauma psychopathology.

References

1. Cha J, Greenberg T, Carlson JM, Dedora DJ, Hajcak G, Mujica-Parodi LR. Circuit-wide structural and functional measures predict ventromedial prefrontal cortex fear generalization: implications for generalized anxiety disorder. J Neurosci. 2014;34(11):4043-53.
2. Galea S, Nandi A, Vlahov D. The epidemiology of post-traumatic stress disorder after disasters. Epidemiol Rev. 2005;27:78-91.
3. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems and barriers to care. US Army Med Dep J. 2008:7-17.
4. Neria Y, Wickramaratne P, Olfson M, Gameroff MJ, Pilowsky DJ, Lantigua R, et al. Mental and physical health consequences of the September 11, 2001 (9/11) attacks in primary care: a longitudinal study. J Trauma Stress. 2013;26(1):45-55.
5. Helzer JE, Robins LN, McEvoy L. Post-traumatic stress disorder in the general population. Findings of the epidemiologic catchment area survey. N Engl J Med. 1987;317(26):1630-4.
6. Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. Mol Psychiatry. 2011;16(6):604-19.
7. Begic D, Jokic-Begic N. Heterogeneity of posttraumatic stress disorder symptoms in Croatian war veterans: retrospective study. Croat Med J. 2007;48(2):133-9.
8. First MB. Diagnostic and statistical manual of mental disorders, 5th edition, and clinical utility. J Nerv Ment Dis. 2013;201(9):727-9.
9. Neria Y. Functional Neuroimaging in PTSD: From Discovery of Underlying Mechanisms to Addressing Diagnostic Heterogeneity. . American Journal of Psyhciaty. 2021;In Press.
10. Biehn TL, Contractor A, Elhai JD, Tamburrino M, Fine TH, Prescott MR, et al. Relations between the underlying dimensions of PTSD and major depression using an epidemiological survey of deployed Ohio National Guard soldiers. J Affect Disord. 2013;144(1-2):106-11.
11. Elhai JD, Naifeh JA, Forbes D, Ractliffe KC, Tamburrino M. Heterogeneity in clinical presentations of posttraumatic stress disorder among medical patients: testing factor structure variation using factor mixture modeling. J Trauma Stress. 2011;24(4):435-43.

12. Naifeh JA, Richardson JD, Del Ben KS, Elhai JD. Heterogeneity in the latent structure of PTSD symptoms among Canadian veterans. Psychol Assess. 2010;22(3):666-74.
13. Lissek S. Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. Depress Anxiety. 2012;29(4):257-63.
14. Lissek S, Rabin S, Heller RE, Lukenbaugh D, Geraci M, Pine DS, et al. Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. Am J Psychiatry. 2010;167(1):47-55.
15. Lissek S, Biggs AL, Rabin SJ, Cornwell BR, Alvarez RP, Pine DS, et al. Generalization of conditioned fear-potentiated startle in humans: experimental validation and clinical relevance. Behav Res Ther. 2008;46(5):678-87.
16. Cooper SE, van Dis EAM, Hagenaars MA, Krypotos AM, Nemeroff CB, Lissek S, et al. A meta-analysis of conditioned fear generalization in anxiety-related disorders. Neuropsychopharmacology. 2022.
17. Fenton AA. Neuroscience. Where am I? Science. 2007;315(5814):947-9.
18. Gilbert PE, Kesner RP, Lee I. Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus. 2001;11(6):626-36.
19. Kim J, Lee I. Hippocampus is necessary for spatial discrimination using distal cue-configuration. Hippocampus. 2011;21(6):609-21.
20. Dunsmoor JE, Prince SE, Murty VP, Kragel PA, LaBar KS. Neurobehavioral mechanisms of human fear generalization. Neuroimage. 2011;55(4):1878-88.
21. Harnett NG, Ference EW, 3rd, Wood KH, Wheelock MD, Knight AJ, Knight DC. Trauma exposure acutely alters neural function during Pavlovian fear conditioning. Cortex. 2018;109:1-13.
22. Kaczkurkin AN, Burton PC, Chazin SM, Manbeck AB, Espensen-Sturges T, Cooper SE, et al. Neural Substrates of Overgeneralized Conditioned Fear in PTSD. Am J Psychiatry. 2017;174(2):125-34.
23. Suarez-Jimenez B, Albajes-Eizagirre A, Lazarov A, Zhu X, Harrison BJ, Radua J, et al. Neural signatures of conditioning, extinction learning, and extinction recall in posttraumatic stress disorder: a meta-analysis of functional magnetic resonance imaging studies. Psychol Med. 2020;50(9):1442-51.
24. Lissek S, Bradford DE, Alvarez RP, Burton P, Espensen-Sturges T, Reynolds RC, et al. Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. Soc Cogn Affect Neurosci. 2014;9(8):1134-42.
25. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013;368(15):1388-97.
26. Lissek S, Kaczkurkin AN, Rabin S, Geraci M, Pine DS, Grillon C. Generalized anxiety disorder is associated with overgeneralization of classically conditioned fear. Biol Psychiatry. 2014;75(11):909-15.
27. Lissek S, Powers AS, McClure EB, Phelps EA, Woldehawariat G, Grillon C, et al. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav Res Ther. 2005;43(11):1391-424.

28. Berg H, Ma Y, Rueter A, Kaczkurkin A, Burton PC, DeYoung CG, et al. Salience and central executive networks track overgeneralization of conditioned-fear in post-traumatic stress disorder. Psychol Med. 2020:1-10.
29. Hammell AE, Helwig NE, Kaczkurkin AN, Sponheim SR, Lissek S. The temporal course of over-generalized conditioned threat expectancies in posttraumatic stress disorder. Behav Res Ther. 2020;124:103513.
30. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018;30(3):383-95.
31. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.
32. Heimberg RG, Horner KJ, Juster HR, Safren SA, Brown EJ, Schneier FR, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. Psychol Med. 1999;29(1):199-212.
33. Shear MK, Frank E, Rucci P, Fagiolini DA, Grochocinski VJ, Houck P, et al. Panic-agoraphobic spectrum: reliability and validity of assessment instruments. J Psychiatr Res. 2001;35(1):59-66.
34. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-7.
35. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
36. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27(9):2349-56.
37. Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. Neuroimage. 2011;55(1):8-23.
38. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. Emotion. 2007;7(2):336-53.
39. Bian XL, Qin C, Cai CY, Zhou Y, Tao Y, Lin YH, et al. Anterior Cingulate Cortex to Ventral Hippocampus Circuit Mediates Contextual Fear Generalization. J Neurosci. 2019;39(29):5728-39.
40. Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci. 2007;27(46):12500-5.

Figures

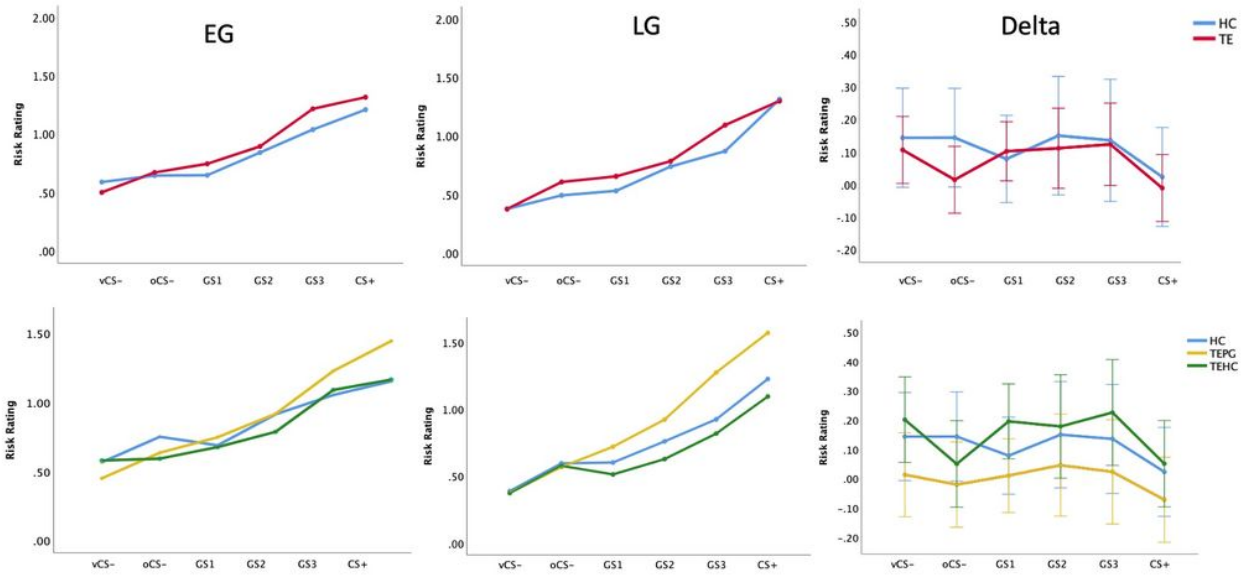

Figure 1

Risk rating in SG phase over time

Abbreviation: TE: trauma-exposed participants; HC: non-trauma-exposed healthy controls ; TEHC: trauma-exposed healthy controls; TEPG: trauma-exposed psychopathology group; EG: early generalization; LG: late generalization

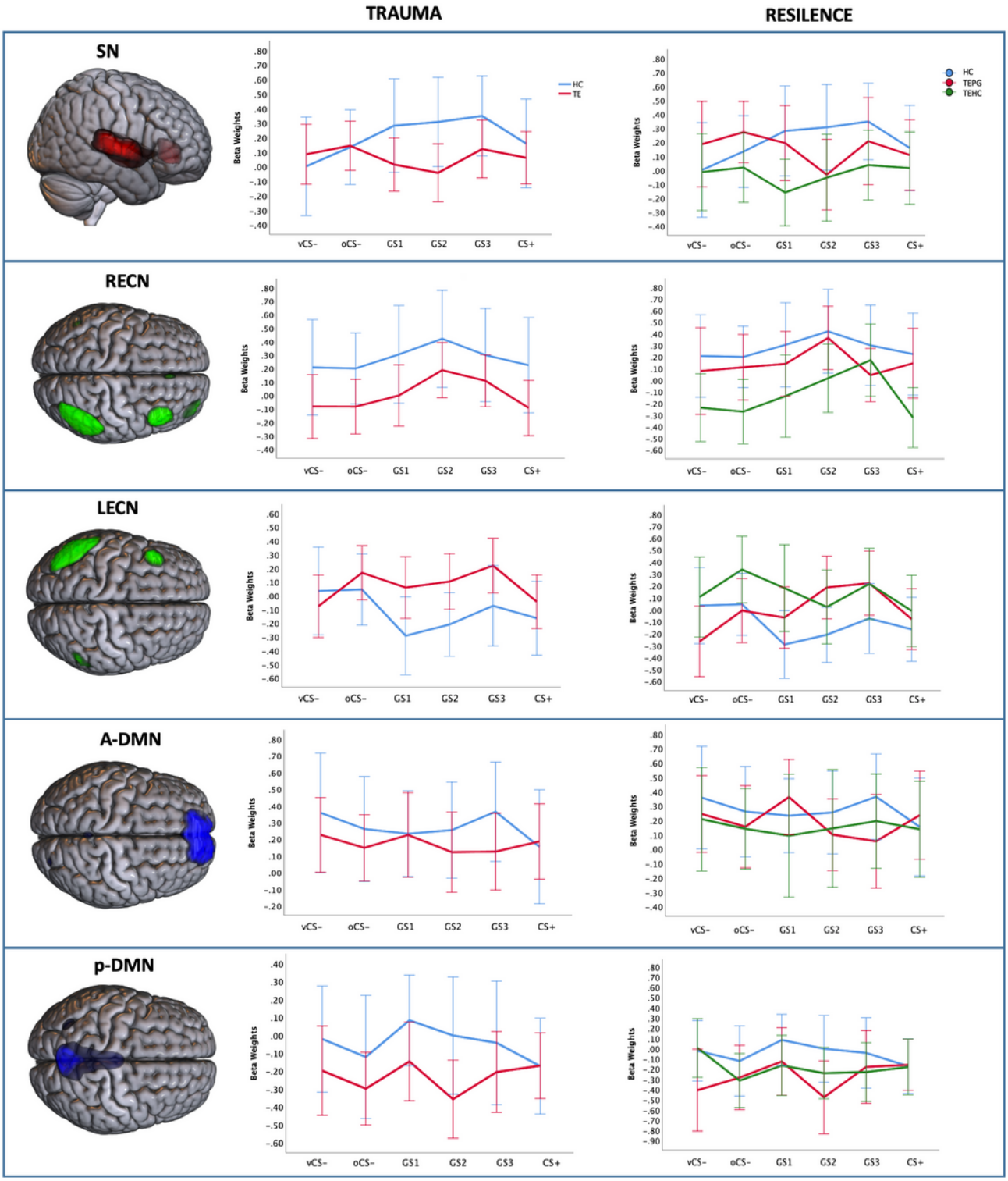

Figure 2

Difference of neural responses to conditioned and generalization stimuli (vCS-, oCS-, GS1, GS2, GS3, CS+) across two stages.

Abbreviation: CS+: conditioned stimuli, danger cue; oCS-: conditioned stimuli, o shape safe cue; vCS-: conditioned stimuli, v shape safe cue; GS: generalization stimuli; SN: salience network; RECN: right

executive control network; LECN: left executive control network; A-DMN: anterior default mode network; p-DMN: posterior default mode network; HC: non-trauma-exposed healthy controls ; TEHC: trauma-exposed healthy controls; TEPG: trauma-exposed psychopathology group.

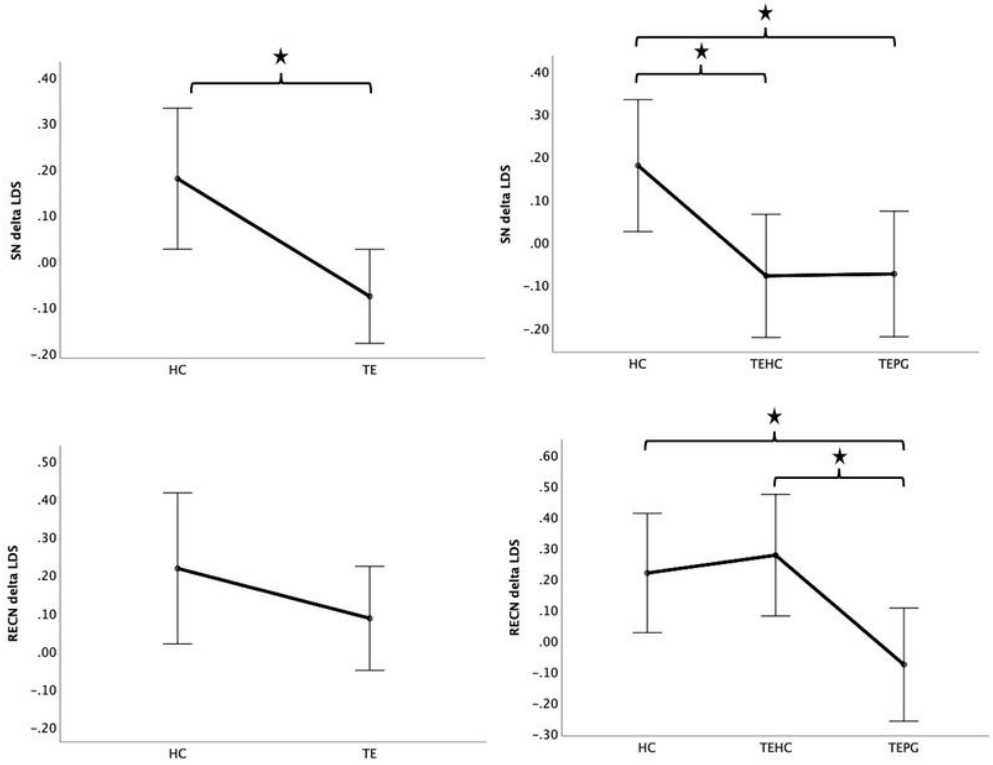

Figure 3

LDS changes in different groups for SN and RECN

Abbreviation: LDS: linear deviation scores; SN: salience network; RECN: right executive control network; HC: non-trauma-exposed healthy controls ; TEHC: trauma-exposed healthy controls; TEPG: trauma-exposed psychopathology group.

Supplementary Files

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