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Early Life Stress Predicts Thalamic Hyperconnectivity: a Transdiagnostic Study of Global Connectivity

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Abstract

Early life stress (ELS) is an established risk factor for psychiatric illness and is associated with altered functional connectivity within- and between intrinsic neural networks. The widespread nature of these disruptions suggests that broad imaging measures of neural connectivity, such as global based connectivity (GBC), may be particularly appropriate for studies of this population. GBC is designed to identify brain regions having maximal functional connectedness with the rest of the brain, and alterations in GBC may reflect a restriction or broadening of network synchronization. We evaluated whether ELS severity predicted GBC in a sample (N=46) with a spectrum of ELS exposure. Participants included healthy controls without ELS, those with at least moderate ELS but without psychiatric disorders, and a group of patients with ELS– related psychiatric disorders. The spatial distribution of GBC peaked in regions of the salience and default mode networks, and ELS severity predicted increased GBC of the left thalamus (corrected $p < .005$, $r = .498$). Thalamic connectivity was subsequently evaluated and revealed reduced connectivity with the salience network, particularly the dorsal anterior cingulate cortex (corrected $p < .005$), only in the patient group. These findings support a model of disrupted thalamic connectivity in ELS and trauma-related negative affect states, and underscore the importance of a transdiagnostic, dimensional neuroimaging approach to understanding the sequelae of trauma exposure.

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CONFLICT OF INTEREST STATEMENT

The authors report no relevant conflicts of interest.

CONTRIBUTORS

Dr. Philip designed the study, wrote the protocol and led the manuscript writing. Ms. Albright and Dr. Almeida drafted the manuscript; Ms. Albright managed the literature searches and participant recruitment. Dr. Sweet designed the imaging protocol. Drs. Tyrka and Price contributed to study conceptualization and design. Dr. Carpenter assisted with study design and facilitated participant recruitment and evaluation. All authors contributed to, and have approved, the final manuscript.

Keywords

early life stress; thalamus; functional connectivity; salience network; dorsal anterior cingulate cortex; default mode network

INTRODUCTION

Early life stress (ELS), often defined as childhood maltreatment, abuse, and neglect, is associated with up to 45% of all childhood-onset and 30% of later-onset psychiatric disorders (Green et al., 2010). There is a transdiagnostic impact of stress exposure during development, as ELS is commonly associated with disorders characterized by negative affect states, such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD), that are often chronic and resistant to treatment (Gilbert et al., 2009; Kaffman & Meaney, 2007; Numeroff et al., 2003; Zeanah et al., 2009).

Characterizing the functional neuroimaging characteristics of adults with prior ELS is an important area of recent research, as it is not completely understood how ELS leads to subsequent illness or psychopathology. Our group and others have reported altered resting state functional connectivity (RSFC) in subjects with a history of ELS and ELS-related disorders. A prominent finding is reduction of RSFC in the default mode network (DMN) (Bluhm et al., 2009; Cisler et al., 2012; Philip et al., 2013; van der Werff et al., 2013). Other key findings include disruptions in emotional processing networks in subjects with ELS. Cisler et al. (2012) found reduced integration between the left amygdala and frontal regions when comparing participants with ELS but without MDD to those with both ELS and MDD (Cisler et al., 2012). RSFC changes within the executive network have also been implicated in ELS; Cisler et al. (2012) reported that dorsolateral prefrontal cortex (DLPFC) connectivity correlated negatively with ELS severity, but did not correlate with MDD symptom severity, and our group recently reported that ELS was associated with greater anti-correlated RSFC between the DLPFC and DMN (Philip et al., 2014), indicating a deterioration in the intrinsic relationships associated with healthy function (Fox et al., 2005). ELS is also associated with reduced negative connectivity between the amygdala and DMN, as well as with decreased RSFC between regions of the salience network and hippocampus (van der Werff et al., 2013). This body of functional connectivity research is complemented by diffusion and morphometry studies of ELS that consistently demonstrate that ELS adversely impacts neural circuits regulating stress response to threatening stimuli. These effects are prominently observed as reductions in corpus callosum integrity, hippocampal size, and reduced volume of the prefrontal cortex, (Reviewed in Teicher & Samson, 2013). Taken together, these findings illustrate that ELS impacts a broad range of cortical and subcortical networks, and indicate a broad-based effect of ELS on multiple intrinsic resting state networks that implies a relationship between this exposure and multiple domains of psychopathology.

These findings have advanced the development of neural circuit-based models of psychiatric illness, and the involvement of multiple networks suggests a central mechanism of disrupted connectivity. The literature reviewed above largely relied upon seed-based approaches to

RSFC, a method that focuses on data from within a single seed voxel or brain region and correlates it with that of all other brain voxels, but may not be sufficient to evaluate broad, multi-network effects. Global-based connectivity (GBC) may be better suited to this application. Based upon graph theory, GBC is a data-driven method that describes the connectivity of each voxel with every other voxel of the brain (Bullmore & Sporns et al., 2009; Cole et al., 2010; Cole et al., 2012; Rubinov & Sporns et al., 2011). As such, changes in GBC can be interpreted to mean a pathological restriction (i.e., reduced GBC) or broadening (i.e., increased GBC) of large-scale network synchronization. GBC therefore may be an ideal method to evaluate exposure, such as ELS, and its impact on voxel inter-connectedness that may be simultaneously affecting multiple intrinsic resting state networks.

To date, few studies have used graph-based analyses in ELS and ELS-related disorders characterized by negative affect. Cisler et al. (2012), described above, used a graph approach to evaluate multiple nodes of the emotional processing network, but this analysis was, by design, restricted to a limited number of brain regions. To our knowledge, only one study has used GBC in MDD: Wang et al. (2014) applied GBC in a sample of MDD patients with or without a history of childhood neglect and matched controls. Compared to controls, the MDD group demonstrated increased global connectivity within the DMN, occipital, and sensorimotor regions. Furthermore, relative to MDD patients without neglect, the MDD group with neglect demonstrated lower global connectivity within the dorsomedial and lateral prefrontal cortex, ventrolateral prefrontal cortex, thalamus, and limbic regions; these reductions were correlated with the severity of childhood neglect. The authors concluded that their findings provided empirical neural evidence of the role of childhood neglect in adult MDD, although the principal limitation of this study was the absence of a group with childhood neglect and without MDD.

In light of these findings, we conducted a study that evaluated whether ELS severity predicted GBC, to investigate whether there might be a central mechanism behind prior observations of disrupted connectivity in ELS and ELS-related disorders. This approach was designed to be transdiagnostic, by including healthy participants with a broad range of ELS and patients with multiple types of trauma-related diagnoses. We hypothesized that ELS would predict disruptions in multiple intrinsic resting state networks, with the most prominent effects observed in our patient sub-sample.

MATERIALS AND METHODS

Participants and Measures

MRI images from 46 right-handed participants were used for this study. This sample represents an imaging database comprised of subjects enrolled in studies of ELS, MDD and PTSD at Brown University-affiliated hospitals. This group included $n = 18$ medication-free healthy controls (ELS-/DIS-), $n = 14$ medication-free participants with ELS and without psychiatric disorders (ELS+/DIS-), and $n = 14$ patients with trauma-related disorders associated with negative affect states (ELS+/DIS+). Data from a portion of these participants have been previously reported (Philip et al., 2014), but no analyses in this study have been previously performed. Participants received diagnostic interviews using the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 1994). Severity of childhood

maltreatment was measured using the Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998). Inclusion criteria for the ELS+/DIS- group required a report of physical, emotional, or sexual abuse as a child, operationally defined as a score of at least “moderate/severe” on any of the five CTQ subscales (i.e., emotional, physical, or sexual abuse, emotional or physical neglect); participants meeting criteria for MDD, PTSD, or any other major Axis I diagnosis were excluded. Inclusion in the ELS+/DIS+ group required meeting criteria for both MDD and PTSD, with currently active symptoms of both disorders and sufficient symptom severity to warrant an illness rating of at least moderate severity on the Inventory of Depressive Symptoms, Self-Report (IDSSR) (Rush et al., 2003) and the PTSD checklist (PCL) (Weathers et al., 2013). Participants in this group did not have to meet a particular threshold of childhood trauma for inclusion. The ELS-/DIS- group was defined by the absence of childhood trauma, confirmed with the CTQ, and absence of any major Axis I diagnosis. Participants in the ELS- and ELS+/DIS- groups were required to be free from any psychotropic medication, whereas participants in the ELS+/DIS+ group were required to be stable on their medications for at least 6 weeks prior to MRI scanning. Exclusion criteria for all groups were standard MRI contraindications and any uncontrolled or active medical illness that could compromise neuroimaging results. Negative urine toxicology screens (and pregnancy tests, when appropriate) were required prior to scanning for all participants. Analysis of variance (ANOVA) was used to examine potential group differences in demographic and associated variables in SPSS (v21, Armonk, NY), followed by post-hoc comparisons to identify between-group demographic differences. Institutional Review Boards of Brown University, Butler Hospital, and the Providence VA Medical Center approved this study. All procedures were conducted in accordance with the Declaration of Helsinki, and all participants provided voluntary written informed consent following full explanation of study procedures.

Image Acquisition

Neuroimaging data were acquired at the Brown University MRI Research Facility (mri.brown.edu) using a Siemens TIM TRIO 3T scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. Whole-brain high-resolution (1 mm³) T1 images were acquired for anatomic reference (TR = 1900ms, TE = 2.98ms, and FOV 256mm²). Resting state echoplanar images were acquired for 8 minutes, during which participants were instructed to remain awake and observe a white fixation cross against a black background (TR = 2500ms, TE = 28ms, FOV = 192mm², and matrix size 64² in 3-mm axial slices; this sequence yielded a total of 192 whole brain volumes with spatial resolution of 3 mm³/voxel).

Image Preprocessing

All preprocessing and imaging data analyses utilized the Analysis of Functional NeuroImages (AFNI) (Cox, 1996), unless otherwise indicated. After image acquisition, anatomic data were transformed to standard Talairach stereotaxic space (Talairach & Tournoux, 1988). Echoplanar data were slice-time corrected and reconstructed into 3D + time datasets, which were concatenated and registered to the fourth volume of the first series to minimize movement artifact. TRs with head motion >1.5mm (informed by Posner et al., 2013) or >10% outliers were censored during preprocessing, and any participants with <

85% retained time points were excluded *a priori*. Bandpass filtering was performed at $.009 < f < 0.08$ to reduce the effect of high-frequency noise and low-frequency drift, and functional data were scaled to normalize within-run intensity. Nuisance variables for each voxel included average ventricle and white matter time series, and six-parameter estimates of head motion (demeaned and derivative values). The predicted time course of these nuisance variables was subtracted from the full voxel time series to yield a residual time series. Smoothing up to a 6mm FWHM Gaussian distribution was performed after preprocessing. Global signal regression was not implemented due to the concern that this preprocessing step may spuriously influence anticorrelations (Murphy et al., 2009; Fox & Greicius, 2010; Saad et al., 2012).

Due to concern about the effect of head motion on RSFC results (Satterthwaite et al., 2012; Power et al., 2012; van Dijk et al., 2012), in addition to censoring TRs with motion and outliers during preprocessing, we evaluated the bivariate correlation between head motion and CTQ score, and compared head motion between the three groups. These analyses were performed using a combination of AFNI and SPSS, and found no significant correlation between CTQ and head motion, and no significant group differences in head motion (see supplemental information).

Global-Based Connectivity

We used GBC methods based on prior studies (Cole et al., 2012; Anticevic et al., 2014). First, for each participant, gray matter masks were generated using automatic segmentation in Freesurfer (v.5.3; surfer.nmr.mgh.harvard.edu). We used the same software version, workstation type and operating system for all participants (Gronenschild et al., 2012). Only gray matter in which >85% of participants had non-zero voxels (defined by their freesurfer segmentation) were used in subsequent steps (see supplemental information). GBC was calculated within AFNI (using the command *3dTCorrMap*), which computed the connectedness of each voxel in the brain with every other voxel in the brain, within gray matter masks. Fisher-transformed correlation values of GBC served as the principal unit for subsequent analysis. We initially performed a one-sample, voxel-wise t-test to describe the spatial distribution of GBC, which was followed by a predictor analysis, where we evaluated those voxels in the brain where CTQ score significantly predicted GBC, (using age, gender, and IDSSR score as *a priori*-defined covariates in the model) within AFNI. Output from the latter analysis provided an estimate of the unique variance associated with CTQ score, when controlling other variables and corrected for multiple comparisons. Because of the concern that pharmacology might influence imaging results (Lanius et al., 2010) we converted medication doses into imipramine equivalents (Bollini et al., 1999; Jakubovski et al., 2016), and used this as a covariate in a sensitivity analysis to estimate the impact of medication load on GBC. Voxel-wise GBC analyses were thresholded at Family-Wise Error (FWE)-corrected $p < .05$ ($Z > 2.33$, cluster size > 64 voxels). The Z threshold was informed by prior studies of GBC (Anticevic et al., 2014), with empiric correction for the cluster size. This multiple comparison correction was generated with AFNI's ClusterSim program, which uses 10,000 Monte Carlo simulations to generate corrections based on height and cluster extents, using a group-appropriate matrix and smoothness of the data. Positive and negative GBC clusters were considered separately within ClusterSim to avoid potentially cancelling out

opposing connectivity. This dimensional (i.e., inclusive of a range of ELS severity), transdiagnostic (i.e., inclusive of MDD and PTSD) GBC approach was the primary outcome measure of this study.

To interpret the GBC results, any brain region identified by this predictor analysis was explored using a traditional seed-based functional connectivity (following methods used in Philip et al., 2014). This approach was designed to describe differences in RSFC between the three participant groups (i.e., ELS-/DIS-, ELS+/DIS-, ELS+/DIS+). First, we saved the spatial extent of the GBC findings as a binary mask, extracted the average BOLD time series within this mask, and then used voxel-based general linear modeling (GLM) to quantify the relationship between the seed and all other voxels in the brain. GLM results yielded individual R^2 values for time series data, which were normalized into Z scores of connectivity, and independent samples *t*-tests were used to compare RSFC between groups. These contrasts were controlled for *a priori* covariates age, gender and depressive symptom severity. Results of all group contrasts were thresholded at FWE-corrected $p < .05$, utilizing the height and cluster correction reported above. Z scores of RSFC were extracted from any regions that differed between groups to describe the direction of observed effects.

RESULTS

Participants

Demographics are reported in Table 1. The ELS+/DIS+ group was significantly older than the other two groups, who did not differ in age, and there was a non-significant trend towards more females in the ELS-/DIS- and ELS+/DIS- groups. ELS+/DIS+ participants were on psychiatric medications used for MDD and PTSD, inclusive of first- and second-line therapeutic agents in multiple classes (see supplemental information for descriptions of psychopharmacology and psychiatric comorbidity). As expected, CTQ severity was greater in the ELS+/DIS+ and ELS+/DIS- compared to ELS-/DIS-, and no significant differences in CTQ score were observed between the ELS+/DIS- and ELS+/DIS+ groups. Comparable distributions of ELS sub-types were observed in both ELS+/DIS- and ELS+/DIS+ groups, except for physical neglect, which differed significantly across groups, with the most frequent reports occurring in the ELS+/DIS+ group. As expected, IDSSR score was highest in the ELS+/DIS+ group.

Global-Based Connectivity

Initial one-sample *t*-tests revealed a broad distribution of GBC that peaked in the right parahippocampal gyrus (BA 19) and left insula (BA 13) (Figure S1). CTQ significantly predicted increased GBC within a 94-voxel cluster located in the left thalamus (corrected $p < .005$) (Figure 1). CTQ score accounted for 24.8% of the variance (partial correlation $r = .498$; $p < .001$) (Figure 2). This effect persisted even when not controlling for age ($r = .422$, $p = .004$). When performing a sensitivity analysis on the effect of medications on these results, the outcome was nearly identical, with a 71-voxel cluster in the same location (corrected $p = .025$); no unique effects of medication were observed. When we explored whether any individual sub-types of ELS were associated with this thalamic finding, results from

emotional neglect and sexual abuse nominally survived correction for multiple comparisons (both corrected $p = .05$). There was no correlation between IDSSR score and GBC ($p > .1$).

Exploring Increased Thalamic RSFC: Comparing Participant Groups

In the contrast of ELS+/DIS- vs. ELS- there was significantly positive RSFC in the ELS +/DIS- group between the thalamus and lingual gyrus (corrected $p < .005$), and right middle temporal gyrus (corrected $p < .05$). For the contrast ELS+/DIS+ vs. ELS-/DIS-, there was significantly positive RSFC in the ELS+/DIS+ group between the thalamus and left postcentral gyrus (corrected $p < .01$), and when comparing ELS+/DIS+ vs. ELS+/DIS-, the ELS+/DIS+ group had significantly negative RSFC between the thalamus and two regions of the salience network (defined by Shirer et al., 2012), the bilateral dorsal anterior cingulate (dACC) (corrected $p < .005$) and left cerebellar culmen (corrected $p < .005$), as well as within the cerebellar vermis extending into the left nodule (corrected $p < .05$) (Table 2) (Figure 3A-C). Negative thalamus to dACC connectivity was also observed in the ELS+/DIS+ vs. ELS-/DIS- contrast, which survived correction for height ($Z = -2.37$), although not cluster ($k = 25$ voxels). Observed effects were due to opposite direction in connectivity in almost all participant group contrasts, except in the ELS+/DIS- vs. ELS+/DIS+ where the dACC result reflected attenuated positive connectivity (Figure 4A-C).

DISCUSSION

Using a data-driven global connectivity approach, we found that the severity of childhood trauma predicted thalamic hyperconnectivity in a transdiagnostic sample inclusive of healthy controls, an intermediate phenotype (ELS exposure but without disorder), and a disorder group composed of the two major psychiatric diagnoses associated with childhood trauma. These results may shed light on imaging correlates of childhood trauma, and provide a theoretical explanation for the neural network disruptions associated with ELS- and related disorders observed in prior imaging studies.

Our finding of increased thalamic GBC is consistent with previous reports in MDD and PTSD. Multiple groups have reported increased thalamocortical connectivity or increased thalamic activity in MDD. Greicius et al. (2007) first reported that increased thalamocortical activity was associated with MDD, and Lui et al. (2011) later reported disruptions in functional connectivity between thalamic and prefrontal regions. A meta-analysis of imaging findings in MDD also found increased resting cerebral blood flow in the thalamus (Hamilton et al., 2012), although Wang et al. (2014) found results in the opposite direction, with reduced GBC in the thalamus in their sample of MDD patients with neglect. It is possible that different types of trauma impact GBC, as we found that emotional neglect and sexual abuse were important components of GBC effects. Altered thalamic connectivity has also been found in PTSD. Ramage et al. (2013) conducted a meta-analysis of trauma processing in PTSD and found important thalamic mediation of emotional processing in PTSD. Zhong et al. (2014) found increased localized subcortical connectivity inclusive of the thalamus, and Lanius et al. (2005) reported increased connectivity between the ventrolateral thalamus and frontal regions, and between the DMN and insular cortex, during PTSD-related dissociation symptoms. Taken together, the results reported here and the prior literature in

MDD and PTSD support the notion of that changes in thalamic connectivity may be a shared trait between psychiatric disorders and prior ELS, suggesting that thalamic hyperconnectivity might represent a marker of earlier exposure.

One important question is how to place these findings in the broader context of the literature. A central thalamic function is to regulate the oscillatory pattern of cortical networks (Buzsaki et al., 2004). Since correlational RSFC methods depend upon the oscillatory pattern of the BOLD time series, it is possible that changes in thalamic oscillations, observed here as increased GBC, may have led to our previous results of reduced DMN RSFC (Philip et al., 2013) and altered RSFC between the DMN and executive networks (Philip et al., 2014). This interpretation is consistent with the theory of thalamocortical dysrhythmia (TCD) proposed by Llinas et al. (1999), in which abnormal thalamic oscillations adversely affect the frequency domains of neural networks. TCD is hypothesized to underlie several neuropsychiatric disorders, including those associated with ELS (Schulman et al., 2011), and it is possible that the observed increase in thalamic GBC may represent an imaging correlate of TCD. While this interpretation remains speculative, it is supported by work by Hamilton et al. (2015), which postulated that aberrant thalamic activity within the DMN could result in a shift of this network into pathological rumination by creating connections between the DMN and subgenual anterior cingulate. Future multimodal imaging studies, combining functional connectivity and thalamic signaling (i.e., magneto-encephalography) would be potential approaches to further evaluate this hypothesis.

Results from our follow-up seed-based exploratory analysis provide insight into the impact of altered GBC. Most remarkable was the contrast between the ELS+/DIS- and ELS+/DIS+ groups, which found reduced connectivity between the thalamus and dACC. The dACC plays a well-known role in error detection/conflict monitoring (Ridderinkhof et al., 2004; Bush et al., 2000) and reward-based decision-making (Bush et al., 2002). From the perspective of neural networks, this area is a hub in both the salience network and DMN (Sheline et al., 2009; Shirer et al., 2012), and is a key area in the “rich club” of brain regions that mediate within- and between network information flow (van den Heuvel & Sporns, 2013). This is aligned with the extensive body of prior work that found abnormal dACC function in both PTSD and MDD (Hamilton et al., 2012; Kaiser et al., 2015; Lei et al., 2015; reviewed in Patel et al., 2012). Our results indicate that disruption of the dACC may constitute a crucial threshold associated with development of clinical symptoms, mediated by pathologically increased thalamic GBC. This explanation would suggest that, in patients with ELS-related disorders, the thalamus is over-connected to the cortex, and a consequence of this over-connectedness is a reduction in needed connectivity with the dACC. This interpretation is consistent with the literature linking ELS with reduced pruning during development (reviewed in McEwen et al., 2015).

Other brain regions implicated in the significant group contrasts are consistent with other studies of trauma-related disorders. For example, multiple groups have reported trauma-related changes to the medial temporal gyrus, with its putative role in integrating memory function and imagery (e.g., Shin et al., 2001; Dickie et al., 2008; Moores et al., 2008). The lingual gyrus, with its likely role in visual processing and integration, has also been

implicated in imaging studies of depression, conflict resolution, and impaired reward response (Dichter et al., 2009; Kessler et al., 2011; Chechko et al., 2013), whereas the postcentral gyrus has been associated with depression and pain (Bar et al., 2007). Taken together, we interpret this to mean that thalamic hyperconnectivity is associated with broad-based disruptions between important brain functions, inclusive of salience, memory and visual processing and sensation, that corresponds to both the literature and our clinical experience with this population. Future longitudinal studies should evaluate the predictive validity of this multi-network matrix as a risk marker of future clinical illnesses and potential target for intervention.

This study has several limitations. As with any study using novel methods, replication will be needed to confirm the reported results. This study also included a modest sample size, particularly for subgroup analyses, and small studies can produce inflated effect sizes (Yarkoni, 2009). That stated, the results obtained from whole-brain evaluations of GBC matched connectivity patterns of intrinsic neural networks and were congruent with prior findings from similar samples. Unfortunately, no participants in the DIS+ group had low CTQ scores, which would have allowed a more nuanced analysis regarding the effects of childhood vs. adult trauma, as prior work has indicated differential sequelae of these exposures (Birn et al., 2014). While both ELS- and ELS+/DIS- groups in this study were medication-free, the ELS+/DIS+ group was taking medications, and as such we are unable to separate illness status from the confounding effect of pharmacotherapy. While medications themselves may impact neuroimaging (e.g., as discussed in Lanius et al., 2010), the fact that participants had active psychiatric symptoms despite stable pharmacotherapy, and modest impact of medication as a covariate suggests an attenuated effect of medications on observed results. DIS+ participants were older, which was expected as these disorders by definition occur over time, and it is possible that imaging results were confounded by age, although we *a priori* statistically adjusted for this variable; sensitivity analysis showed increased thalamic GBC remained strongly significant when not adjusting for age. Prior work has revealed reduced thalamus to salience network connectivity associated with healthy aging (Cao et al., 2014), although this reduction was seen in older participants than in our sample, and was not evaluated in the context of childhood trauma. Other limitations include those inherent to cross-sectional studies and retrospective self-reports of ELS.

In summary, this study found that ELS predicted increased thalamic global connectivity, which can explain previous observations of multiple network disruption. This work suggests thalamic hyperconnectivity may be a shared trait across ELS-related psychiatric disorders, and may represent an imaging biomarker of threshold exposure. Future work is needed to further evaluate its utility as a diagnostic marker of prior exposure, or as a potential predictor of treatment response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Severity of childhood trauma predicts increased thalamic global-based connectivity. Image is shown using radiologic convention and Z coordinates (Talairach) are shown on the bottom left. Image is corrected $p < .05$. Color bars represent Z scores.

Figure 2. Scatterplot of correlation between strength of thalamic seed global based connectivity and severity of childhood trauma, adjusted for age, gender and depressive symptom severity. Partial correlation $p < .001$. Key: GBC, global-based connectivity; CTQ, childhood trauma questionnaire score.

Figure 3A-C.

Group contrasts comparing A) ELS+/DIS- vs. reference ELS-, showing increased RSFC from the thalamus to the lingual gyrus and medial temporal gyrus, B) ELS+/DIS+ group vs. reference ELS- group, showing increased RSFC to the postcentral gyrus, and C) ELS+/DIS+ group vs. reference ELS+/DIS- group showing reduced RSFC to the dorsal anterior cingulate and vermis. The cerebellar culmen result is not displayed. Images are shown using radiologic convention and Z slice coordinates (Talairach) are shown on the bottom left of the corresponding image, except for C that uses X slice coordinates. Images are corrected $p < .05$.

A **Figure 0004****B** **Figure 0005**

Figure 0006**Figure 4A-C.**

Bar graphs of connectivity strength, illustrating the directions of effect of observed changes in RSFC, in regions that significantly differed between groups. Y-axis refers to Z scores of connectivity. Letters correspond to contrast images shown in Figure 3A-C.

Table 1

Demographic Characteristics (N = 46)

Characteristic	ELS-/DIS- (n = 18)	ELS+/DIS- (n = 14)	ELS+/DIS+ (n = 14)	F	P
Age (Mean $\pm$ SD years)	32 $\pm$ 9	37 $\pm$ 10	51 $\pm$ 13	12.31	< .001 ^a
Gender (n, % Female)	11 (61)	7 (50)	4 (29)	1.71	.194
College Education (%)	61	64	43	.54	.584
CTQ Score (Mean $\pm$ SD)	22 $\pm$ 15	59 $\pm$ 16	64 $\pm$ 9	43.79	< .001 ^b
CTQ Sub-Scale (Mean $\pm$ SD)					
Emotional Abuse	5 $\pm$ 4	12 $\pm$ 4	14 $\pm$ 5	21.62	< .001 ^b
Physical Abuse	4 $\pm$ 3	11 $\pm$ 5	13 $\pm$ 6	15.50	< .001 ^b
Sexual Abuse	4 $\pm$ 3	12 $\pm$ 8	10 $\pm$ 5	10.48	< .001 ^b
Emotional Neglect	6 $\pm$ 4	14 $\pm$ 4	14 $\pm$ 6	19.49	< .001 ^b
Physical Neglect	4 $\pm$ 3	10 $\pm$ 4	13 $\pm$ 2	33.90	< .001 ^c
IDSSR Score (Mean $\pm$ SD)	2 $\pm$ 2	10 $\pm$ 6	49 $\pm$ 11	180.42	< .001 ^c

Key: ELS, early life stress; DIS, disorder; SD, standard deviation; CTQ, Childhood Trauma Questionnaire; IDSSR, Inventory of Depressive Symptoms, Self-Report

^a significant at $p < .001$ across groups, no difference observed between ELS-/DIS- and ELS+/DIS- groups.

^b significant at $p < .001$ across groups, no difference observed between ELS+/DIS- and ELS+/DIS+ groups.

^c significant at $p < .001$, with statistically significant differences observed between all groups.

Table 2

Group Contrasts: Thalamic RSFC of Participant Groups

ELS+/DIS- vs. ELS-/DIS-				
Region	BA	Peak Coordinates	Cluster Size	Z Score
Bilateral Lingual Gyrus	18	-4, -70, 5	93	3.2
R Middle Temporal Gyrus	37	41, -58, -4	66	3.0
ELS+/DIS+ vs. ELS-/DIS-				
Region	BA	Peak Coordinates	Cluster Size	Z Score
L Postcentral Gyrus	4	-61, -13, 20	85	3.0
ELS+/DIS+ vs. ELS+/DIS-				
Region	BA	Peak Coordinates	Cluster Size	Z Score
Bilateral dACC	24/32	-1, -1, 47	100	-3.2
L Culmen	-	-34, -49, -22	93	-4.6
L Nodule / Vermis	-	-1, -43, -34	67	-3.7

Key: ELS, early life stress; DIS, disorder; R, right; L, left; dACC, bilateral dorsal anterior cingulate cortex. Results from group contrasts, corrected at $p < .05$. For each comparison, the second group served as the reference (i.e., contrasts of ELS+/DIS- vs. ELS-/DIS- used ELS-/DIS- as the reference group).