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Regional homogeneity and resting state functional connectivity: associations with exposure to early life stress

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Abstract

Early life stress (ELS) confers risk for psychiatric illness. Previous literature suggests ELS is associated with decreased resting-state functional connectivity (rs-FC) in adulthood, but there are no studies of resting-state neuronal activity in this population. This study investigated whether ELS-exposed individuals demonstrate resting-state activity patterns similar to those found in PTSD. Twenty-seven adults (14 with at least moderate ELS), who were medication-free and without psychiatric or medical illness, underwent MRI scans during two 4-minute rest periods. Resting-state activity was examined using regional homogeneity (ReHo), which estimates regional activation patterns through indices of localized concordance. ReHo values were compared between groups, followed by rs-FC analyses utilizing ReHo-localized areas as seeds to identify other involved regions. Relative to controls, ELS subjects demonstrated diminished ReHo in the inferior parietal lobule (IPL) and superior temporal gyrus (STG). ReHo values were inversely correlated with ELS severity. Secondary analyses revealed decreased rs-FC between the IPL and right precuneus/posterior cingulate, left fusiform gyrus, cerebellum and caudate in ELS subjects. These findings indicate that ELS is associated with altered resting-state activity and connectivity in brain regions involved in trauma-related psychiatric disorders. Future studies are needed to evaluate whether these associations represent potential imaging biomarkers of stress exposure.

Keywords

posttraumatic stress disorder; resting state activity; inferior parietal lobule; superior temporal gyrus

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CONFLICT OF INTEREST

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1. Introduction

Early life stress (ELS) may include physical, sexual or emotional abuse, malnourishment, and physical or emotional neglect (Leeb et al., 2008), and is a common phenomenon (U.S. Department of Health and Human Services, 2007). ELS is a risk factor for a variety of psychiatric illnesses, including posttraumatic stress disorder (PTSD), major depressive disorder (MDD), and borderline personality disorder. There is a growing body of evidence that individuals with a history of ELS, even without a diagnosable psychiatric illness, demonstrate neurobiological abnormalities thought to represent sequelae of ELS exposure. This has been shown using a variety of different methodologies, including neuroendocrine (Carpenter et al., 2007; Carpenter et al., 2009; Tyrka et al., 2009) and epigenetic (Tyrka et al., 2012) approaches. Neuroimaging has also been a fruitful method to evaluate structural and functional correlates of ELS. Structural studies have demonstrated decreased volumes of the prefrontal cortex, hippocampus, and corpus callosum associated with a history of ELS exposure, while functional imaging studies of this population have found a negative attention bias, and altered amygdala, posterior insula, and dorsal anterior cingulate function during cognitive and emotional processing tasks (for a comprehensive review, see (Hart and Rubia, 2012)).

Recently, resting state functional connectivity (rs-FC) has been increasingly utilized to characterize neuroimaging correlates of ELS exposure. Data acquired during the resting state (i.e., task-free) provides complementary data to standard task-associated fMRI studies (Cole et al., 2010), as both states are likely relevant to psychiatric illness. While the precise relationship between resting state and task-associated activations is still under investigation, it is thought that rs-FC represents underlying patterns of coordinated brain activity (Di and Biswal, 2012). A variety of approaches have been used to focus rs-FC investigations, such as seed-based correlation, independent component analysis and measurement of the amplitude of low-frequency fluctuations. Each approach has merits (reviewed in (Biswal et al., 2010)), and in general rs-FC is relatively easy to implement and may be well suited to clinical use (Fox and Greicius, 2010). To date, ELS has been associated with several findings, including diminished rs-FC within the default mode network (DMN) in individuals with PTSD from ELS (Bluhm et al., 2009), as well as altered connectivity associated with executive and emotion-regulating networks in patients with MDD and a history of ELS (Cisler et al., 2012). One kind of ELS, emotional maltreatment, has been associated with diminished negative connectivity between the amygdala and precuneus, as well as with decreased rs-FC between the insula and hippocampus (van der Werff et al., 2012). Our group also reported that ELS, in the absence of other psychiatric symptoms, was associated with diminished rs-FC within the DMN and increased rs-FC between the amygdala and medial prefrontal cortex (MPFC) (Philip et al., 2013). Taken together, these findings support a relationship between ELS exposure and impaired rs-FC.

Despite the growing body of evidence that effects of ELS exposure may be observable in rs-FC measures, to date there have been few studies that qualitatively evaluate resting state *activity* patterns with brain imaging methods in ELS-exposed samples. This is an important deficiency in the literature, as resting state activity may provide a method to better interpret the relationship between traditional task-associated functional MRI data and resting state (i.e., task-free) connectivity findings. Results from older studies of subjects with PTSD that quantitatively measured brain activity, such as single-proton emission computed tomography (SPECT), were mixed. One study found decreased cerebral blood flow to the caudate (Lucey et al., 1997), whereas others found increased flow to the caudate, anterior and posterior cingulate and hippocampal regions (Sachinvala et al., 2000) or increased blood flow to the superior temporal gyrus, fusiform gyrus, and cerebellum (Bonne et al., 2003).

A novel method to evaluate resting state activity is through estimation of regional homogeneity (ReHo). First applied by Zang et al. (2004), this data-driven method is based on the theory that the BOLD signal fluctuations in a given region reflect adjacent neuronal activity occurring at the same frequency, and this temporal synchrony is confined to populations of neurons performing a related function. Kendall's coefficient of concordance (KCC) (Kendall and Gibbons, 1990), a nonparametric correlation method, is used to calculate a summary index of temporal synchrony within an individual and neighboring voxels, providing an estimation of the efficiency of coordinated neuronal activity. Higher ReHo is thought to indicate greater temporal synchrony, whereas lower values are thought to represent decreased local coherence.

The ReHo approach has been applied to evaluate resting state cortical activity in several psychiatric disorders, including MDD (Guo et al., 2011; Guo et al., 2012; Liu et al., 2012b), bipolar disorder (Liu et al., 2012a), sleep disorders (Dai et al., 2012), and substance dependence (Liao et al., 2012; Tang et al., 2012). One investigation relevant to the current study utilized ReHo to evaluate resting state activity in PTSD (Yin et al., 2012). In this study, the authors imaged PTSD participants and traumatized controls without PTSD, all of whom had been exposed to the 2008 Sichuan earthquake. Relative to controls, PTSD subjects demonstrated increased ReHo in the inferior parietal lobule (IPL) and right superior frontal gyrus, and reduced ReHo in the right middle/superior temporal gyrus (STG) and lingual gyrus. Based on their findings and previous PTSD research, they concluded that alterations in localized activity might contribute to neural mechanisms of PTSD, through increased coherence of attention networks and decreased coherence in visual identification and emotion systems. Unfortunately, this study did not report medication exposure, which is an important consideration in imaging studies (Lanius et al., 2010), or previous (i.e., pre-earthquake) trauma exposure.

While the previous study provides data on resting state activity associated with PTSD, the lack of a nontraumatized control group prevents inferences regarding the effects of prior ELS. This is an important issue, since multiple previous studies have demonstrated that prior ELS exposure is a powerful prognostic indicator of those who will develop PTSD (Cabrera et al., 2007; Iversen et al., 2008; Berntsen et al., 2012), and trauma-exposed healthy controls have been used in imaging studies of PTSD to account for this potential confound. To our knowledge, the present study is the first to examine ReHo in a sample of medication-free, ELS-exposed individuals without psychiatric illness in comparison to individuals without trauma exposure. Study of such individuals, using resting state activity methods, can inform the field's understanding of the neural correlates of stress exposure and facilitate the accuracy of future resting state studies of PTSD. Based on the studies reviewed above, we hypothesized that, similar to patients with PTSD, healthy subjects with a history of ELS would exhibit increased ReHo in the inferior parietal lobule and superior frontal gyrus and decreased ReHo in the superior temporal gyrus and lingual gyrus.

2. Methods

2.1. Participants

Participants with a reported history of ELS exposure ($n = 14$) and healthy controls ($n = 13$) were recruited for this study from an ongoing longitudinal study examining potential endophenotypes for mood/anxiety disorders; this group was an expanded sample from our previous study of default network connectivity in 22 participants with and without ELS (Philip et al., 2013). This study was conducted under the approval of the Brown University and Butler Hospital Institutional Review Boards, and participants were reimbursed \$50 for their participation.

Study inclusion criteria were 1) a history of physical, emotional, or sexual abuse as a child, defined as a Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998) subscale classification score of “moderate/severe” or “severe/extreme” (ELS group), or absence of such history confirmed with the same instrument (control group), and 2) absence of a current Axis I or Axis II psychiatric disorder, assessed by the Structured Clinical Interview for DSM-IV-TR (SCID and SCID II) (First, 1994). ELS severity was assessed via the CTQ, a 28-item self-report measure that asks respondents to recollect the frequency of childhood experiences of abusive and neglectful behavior using a 5-point Likert-type scale (“never true,” “rarely true,” “sometimes true,” “often true,” or “very often true”). The scores of items corresponding to five different types of maltreatment (emotional, physical, and sexual abuse, and emotional and physical neglect) are summed to produce scale scores that represent the severity of ELS in each area, and then organized by standardized cut-off scores for maltreatment severity (i.e., none to minimal, low to moderate, moderate to severe, and severe to extreme) (Bernstein and Fink, 1998). ELS and control participants were matched on the basis of age and gender. Exclusion criteria were 1) contraindication to MRI scanning (such as bodily inclusion of ferromagnetic objects), 2) current treatment with psychotropic medications, or 3) active medical illness, assessed by medical history, physical and neurological examination, electrocardiogram, and standard laboratory studies. Participants who reported significant life stress in the previous month, assessed using the Perceived Stress Scale (Cohen et al., 1983), were excluded. A negative pregnancy test for women of childbearing age was required before MRI exposure.

2.2. Image acquisition

All neuroimaging data were acquired at the Brown University MRI Research Facility (www.brainscience.brown.edu/MRF) using a Siemens TIM TRIO 3 Tesla scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. During the scan session participants were instructed to remain awake and watch a white fixation cross against a black background. Images were acquired during two separate 4-minute epochs. Acquisition parameters for echoplanar images were TR = 2500 ms, TE = 28 ms, FOV = 192 mm², and matrix size 64² in 3-mm axial slices. This sequence yielded two functional imaging runs of 96 TRs for a total of 192 whole brain volumes, with spatial resolution of 3 mm³ per voxel. Whole-brain high-resolution (1 mm³) T1 images were acquired prior to resting state scans for anatomic reference. Acquisition parameters for these images were TR = 1900 ms, TE = 2.98 ms, and FOV 256 mm².

2.3. Image preprocessing

After image acquisition, anatomic data were transformed to standard Talairach stereotaxic space (Talairach, 1988). Echoplanar data were reconstructed into 3D + time datasets, which were concatenated and registered to the sixth volume of the first series to minimize movement artifact and generate motion correction parameters for use as covariates in subsequent analysis. Bandpass filtering was performed at $.0083 \text{ sec} < f < 0.15 \text{ sec}$ to reduce the effect of high frequency noise and low frequency drift. All preprocessing and subsequent data analyses utilized the Analysis of Functional NeuroImages (AFNI) (Cox, 1996) software unless otherwise specified. Global signal regression was not performed due to its potential impact on correlations in resting state data (Saad et al., 2012).

2.4. Head motion analysis

Reflecting the growing concern regarding the impact of participant motion in resting state MRI studies (Satterthwaite et al., 2012; Van Dijk et al., 2012), we evaluated significant differences in head motion between groups using values for a) movements in the x, y, and z direction and b) roll, pitch, and yaw, generated during individual alignment and registration.

In order to compare head motion between groups, we calculated the derivative of the Euclidean norm of motion, yielding an aggregate motion parameter that combined translational (i.e., mm) and rotational (i.e., degrees) values generated during preprocessing. This metric was then compared between groups using analysis of variance (ANOVA), with significance set at two-tailed $P < .05$, using SPSS Statistics 19 (IBM Corporation, Armonk, NY).

2.5. Regional homogeneity calculation

After masking outside of brain data, individual ReHo maps were generated by calculating the KCC, which measures ReHo of the BOLD time series data in each voxel and its 26 nearest contiguous voxels. This was done using AFNI's 3dReHo command. Data were subsequently smoothed using a 4 mm full-width-half-maximum (FWHM) Gaussian kernel.

2.6. Analysis of regional homogeneity and correlations

To evaluate group differences in ReHo values between ELS- and non-exposed participants, we conducted a whole-brain voxel-wise comparison using two-sample t -tests, using the KCC value for each voxel as the dependent measure. Family-wise multiple comparisons correction was performed using AFNI's ClusterSim program, which is based on AlphaSim and uses Monte Carlo simulations to determine required voxel and cluster size for a predetermined alpha level in a given matrix size. Selection of a priori statistical thresholds for this study was guided by those used in the previous Yin et al. (2012) study. Individual voxel significance for two-sample t -tests was set at $P < .001$, with a minimum cluster size of 9 voxels, to yield an FWE-corrected, two-tailed $P < .01$ (hereafter $P_{\text{corrected}}$). To explore the relationship between ELS severity and ReHo, average ReHo values were then extracted from regions that had demonstrated significant differences between groups, and correlations between ELS severity and average ReHo values were calculated using bivariate Pearson r with SPSS. To evaluate the relationship between ReHo and subclinical anxiety or depressive symptoms, anxiety and depression were measured using the State-Trait Anxiety Inventory (STAI) (Spielberg et al., 1983) and Inventory of Depressive Symptomatology Self-Report (IDSSR) (Rush et al., 1986), respectively. IDSSR scores greater than 14 are considered to reflect significant depressive symptoms, whereas a score of 39 is considered to be the cut-off for healthy controls in the STAI. STAI and IDSSR scores were compared between groups and correlated with average ReHo values using bivariate Pearson r in SPSS.

2.7. Seed-based functional connectivity analysis

Following our primary analysis of group differences in ReHo, we performed an exploratory analysis using resting state seed-based connectivity analysis to identify other brain regions affected by changes in ReHo, in order to investigate further group differences. This methodology has been demonstrated to be a robust analytic approach to identify resting state networks (Biswal et al., 2010; Cole et al., 2010; Smith et al., 2010). Utilizing a mask of significant regions from our ReHo analysis, we extracted average time series data from seed regions and utilized voxel-based general linear modeling (GLM) to quantify the relationship between the seed and the rest of the brain. GLM results yielded individual R^2 values for time series data, which were normalized into Z values using Fisher's R -to- Z transformation (Fisher, 1915). Initial one-sample t -tests of these Z values were used to describe the spatial extent of the connectivity with the source seed, and second level independent samples t -tests were used to compare resting state connectivity between ELS- and non-exposed groups. Significance threshold was set at $P_{\text{corrected}} < .05$ for this exploratory analysis using the same multiple comparisons correction generated for the ReHo analysis.

3. Results

3.1. Participants and head motion analysis

Demographics are reported in Table 1. There were no differences between groups in age, gender, or education. Seven of the non-ELS participants reported minor ELS exposure. Within the ELS group, five participants met criteria for any lifetime Axis I condition. With the exception of one participant who had met criteria for lifetime MDD and PTSD, all others were classified as “Not Otherwise Specified” (under DSM-IV-TR), or alcohol abuse. One participant in the non-ELS group met criteria for lifetime alcohol abuse. One participant in the ELS group had head motion greater than 3 mm during the scan session and was subsequently excluded, leaving an evaluable sample of 26 (13 with and 13 without ELS). There were no differences in head motion parameters between groups ($.10 \pm .07$ and $.12 \pm .08$, for ELS and non-ELS groups, respectively; $F = .31$, $df = 1$, $P = .58$).

3.2. ReHo and connectivity analyses

Regions showing significant differences between groups are reported in Table 2. Compared to controls, subjects with a history of ELS had significantly decreased ReHo in the right inferior parietal lobule (IPL) and right superior temporal gyrus (STG) ($P_{\text{corrected}} < .01$) (Figure 1). There were significant negative correlations between average ReHo values and ELS severity ($r = -.57$, $P < .01$ and $r = -.60$, $P < .01$, for the IPL and STG, respectively), however, there was no dose-dependent effect of ELS within the exposed group ($r = -.27$, $P = .37$ and $r = -.37$, $P = .22$). There was a significantly higher mean IDSSR score in the ELS group (10 ± 6 vs. 3 ± 2 , for ELS and non-ELS, respectively, $P < .01$). There were no significant group differences in state anxiety ($P > .1$), while there was significantly greater trait anxiety in ELS participants (33 ± 9 vs. 26 ± 5 , for ELS and non-ELS, respectively, $P = .04$). STAI scores for both groups were below those considered to indicate clinically significant symptoms (Spielberg et al., 1983), and higher IDSSR scores in the ELS group were consistent with mild depressive symptoms (Rush et al., 1986). Average ReHo was not significantly correlated with either subscale of the STAI or IDSSR scores ($P > .1$).

Follow-up exploratory analyses utilized the IPL and STG as seed regions for a serial analysis of whole-brain connectivity. ELS status was associated with decreased functional connectivity between the IPL and the right precuneus/posterior cingulate, fusiform gyrus and declive (cerebellum) ($P_{\text{corrected}} < .01$), as well as the caudate ($P_{\text{corrected}} = .05$). All rs-FC results reflected a decrease in Z scores of connectivity in the ELS group, except the caudate, which demonstrated a negative Z score (Table 3, Figure 2). There were no significant group differences when using the STG seed.

4. Discussion

To our knowledge, this is the first study to evaluate resting state localized brain activity utilizing a ReHo analysis in a sample of unmedicated ELS-exposed individuals without psychiatric or medical illness compared to unexposed controls. Individuals with ELS had decreased ReHo in two principal regions, the right IPL and STG, and decreased ReHo correlated with increased ELS severity. While both these regions have been previously implicated in PTSD, in this ELS sample the direction of effect was reversed in the IPL.

The IPL is thought to be involved in spatial memory and visual-spatial processing (Petersen et al., 1988; Posner et al., 1988; Pardo et al., 1991). It is described as part of the cortical mirror-neuron system (Ocampo et al., 2011), developmentally matures later than other brain regions (Barber et al., 2013), and as such may be susceptible to the neurotoxic effects of stress from longer exposure to excessive glucocorticoid secretion (Patel and Finch, 2002; Conrad et al., 2007). Pathologically, the IPL is involved in the dysregulation of affective

circuitry implicated in depression (Delaveau et al., 2011), has decreased volume associated with stress exposure (Hanson et al., 2010), and may also be implicated in selective attention and hypervigilance associated with PTSD (Morey et al., 2008). This may be a uniquely affected region in PTSD, as, to our knowledge, ReHo studies of MDD (Guo et al., 2011; Guo et al., 2012; Liu et al., 2012b) have not demonstrated altered ReHo in the IPL. To our knowledge, this is the first study to report changes in activity associated with ELS in the IPL. Future longitudinal studies are needed to evaluate how changes in decreased IPL ReHo may be related to psychiatric illness development.

The STG is implicated in the modulation of amygdala activity, and is also thought to be involved in extinction of fear conditioning, episodic memory, and language processing (Brunet et al., 2000). Our results are consistent with previous studies across neuroimaging modalities, which have found decreased ReHo (Yin et al., 2012) and reduced blood flow to this region during symptom provocation in PTSD populations (Bremner et al., 1997; Shin et al., 1997; Bremner et al., 1998). Decreased STG ReHo has been found in MDD subjects (Guo et al., 2011). Taken together, we hypothesize decreased STG ReHo might be related to impairments in amygdala modulation, which may reflect risk for the development of trauma-associated disorders (Parsons and Ressler, 2013).

Results from our seed-based connectivity analysis indicate that regions with diminished ReHo have reduced rs-FC with other brain regions involved in trauma-related disorders. While directionality of effect cannot be determined from this analysis, these results show that in this sample, there is diminished rs-FC between the IPL and multiple brain regions including the precuneus/posterior cingulate, caudate nucleus, fusiform gyrus, and cerebellum.

The precuneus/posterior cingulate is the major posterior node of the DMN and is thought to be involved in self-processing (Raichle et al., 2001; Greicius et al., 2003). Our group has previously shown diminished resting state connectivity of this network in ELS-exposed subjects when using the PCC and amygdala seed regions for functional connectivity (Philip et al., 2013). One interpretation of this result is that in this population (i.e., with ELS but without PTSD), functional connections between the IPL and precuneus may be down-regulated.

The fusiform gyrus is implicated in associative memory and visual processing, and multiple previous studies have demonstrated impaired fusiform activity (Morey et al., 2009; Yin et al., 2012) and connectivity (Wu et al., 2011; Yin et al., 2012) in PTSD as well as in MDD. These impairments in activity and connectivity may underlie symptoms of trauma-related disorders, such as difficulty processing emotional information and attention to negative social cues (Chan et al., 2009).

Reduction in caudate volume (Dannlowski et al., 2012) and increased caudate activity have been associated with PTSD (Linnman et al., 2011), although to our knowledge this is the first study to show diminished connectivity between the IPL and caudate in an ELS sample. The caudate is often associated with learning and memory processing (Packard and Knowlton, 2002), as well as with regulation of information carried between the thalamus and orbitofrontal cortex (Grahn et al., 2008). The caudate, as part of the striatum, is also involved in reward processing and implicated in clinical symptoms of anhedonia in major depression (Keedwell et al., 2005; Epstein et al., 2006) and schizophrenia (Harvey et al., 2010). One interpretation of these results is that decreased connectivity between the IPL and caudate may contribute to dysfunction in learning and reward processing in multiple psychiatric illnesses associated with learning deficits.

We also found decreased IPL-to-cerebellum connectivity associated with ELS. Although the cerebellum is not typically considered part of the fear and anxiety circuitry, there is a growing body of evidence indicating that the cerebellum may be involved in psychiatric illnesses. Previous studies have found decreased cerebellum volume associated with PTSD (Hart and Rubia, 2012), and decreased cerebellar ReHo has been associated with MDD (Liu et al., 2011). Based on these findings, decreased IPL-to-cerebellum activity may contribute to disrupted motor control of emotional processing (Coombes et al., 2009), although we recognize the need for more focused characterization of the role of the cerebellum in ELS and related conditions.

Our study did not detect alterations in the superior frontal and lingual gyrus, both reported by Yin et al. (2012) in patients with PTSD. This may have been due to the reduced psychiatric morbidity in our subjects in comparison with the clinically ill participants in previous studies. Interestingly, neither the previous Yin study nor ours found changes in ReHo in the amygdala or MPFC, both important brain regions consistently implicated in PTSD. This may represent a methodological limitation of ReHo, in that activity in smaller (i.e., less than 27 contiguous voxels) regions may not be detected by this approach. We also did not find a relationship between ReHo values and measures of anxiety or depression, which may reflect the use of a nonclinical sample.

The methods applied in this study merit comment. Although the ReHo analytic technique is relatively new, it provides an estimate of resting state cerebral activity, using correlational methods. Results from ReHo analysis can be easily used to conduct further analysis of involved brain regions, as demonstrated in this study through follow-up rs-FC analyses. Further technical advances will be needed in order to determine the directionality of effect; from our data we cannot state whether changes in ReHo cause altered rs-FC, or vice versa. However, coupled ReHo and rs-FC analyses may allow researchers to further evaluate the relationship between brain activity and connectivity, and this approach may allow for the identification of regions involved in a given condition or illness that might not be visualized by either method alone. Future studies are needed to compare the ReHo approach to other modalities that directly evaluate or quantify cortical activity (i.e., SPECT, PET and arterial spin labeling).

4.1. Limitations

One limitation to our study is that it did not have a clinically ill comparison group. Future studies should compare results from non-exposed individuals, those exposed to ELS without psychiatric illness, PTSD associated with ELS, and MDD associated with ELS. Since our study was cross-sectional in nature, it is possible participants will develop PTSD or other psychiatric disorders in the future. Another limitation is that since participants were selected based on a threshold of ELS exposure, results demonstrating the relationship between ReHo values and correlates of ELS (particularly the relationship between ELS severity and strength of ReHo) must be interpreted with caution. The potential inaccuracies inherent in self-reported ELS constitute a limitation, although this is a broader issue in any cross-sectional study of this population. Lastly, the sample size of the current study is limited, so findings from this report should be interpreted as preliminary.

In summary, we found decreased localized resting state activity in the IPL and STG in association with ELS, and in an exploratory follow-up analysis, diminished rs-FC between the IPL and multiple brain regions previously implicated in trauma-related disorders. Our findings raise the possibility that ELS is associated with diminished ReHo in the IPL and STG, which suggests that at least some of the previous findings of altered ReHo associated with PTSD are due to prior ELS exposure.

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Figure 1.

Group Differences in Regional Homogeneity Comparing Early Life Stress vs. Non-Exposed Controls

Axial images showing regions with decreased regional homogeneity in early life stress (ELS) vs. control participants. Results from independent samples *t*-test are thresholded at family-wise error corrected *P*-value < .05. Images are shown using radiologic convention. Z coordinates of each slice are shown at the bottom left of the corresponding image. A) Inferior parietal lobule, B) superior temporal gyrus.

Figure 2.

Group Differences in IPL-Seed Connectivity Comparing Early Life Stress vs. Non-Exposed Controls

Sagittal images showing regions with decreased resting state connectivity when seeding the inferior parietal lobule, comparing early life stress (ELS) vs. control participants. Results from independent samples *t*-test are thresholded at family-wise error corrected *P*-value < .05. X coordinates of each slice are shown at the bottom left of the corresponding image. A) Right precuneus/posterior cingulate, B) left declive (cerebellum), C) left caudate, and D) left fusiform gyrus.

Table 1

Demographic and Clinical Characteristics

Characteristic	ELS (<i>n</i> = 14)	Control (<i>n</i> = 13)	<i>P</i>
Age (Mean $\pm$ <i>SD</i> years)	37 $\pm$ 10	30 $\pm$ 9	.08
Gender (<i>n</i> , % Female)	7 (58)	9 (69)	ns
College Education (%)	64	50	ns
IDSSR	10 $\pm$ 6	3 $\pm$ 2	< .01
STAI State	30 $\pm$ 8	26 $\pm$ 6	ns
STAI Trait	33 $\pm$ 9	26 $\pm$ 5	.04
CTQ			
Category (<i>n</i> , %) ^a			
Emotional Abuse	4 (29)	-	
Physical Abuse	8 (57)	-	
Sexual Abuse	8 (57)	-	
Emotional Neglect	7 (50)	-	
Physical Neglect	7 (50)	-	
Summary Score (Mean $\pm$ <i>SD</i>) ^b	7 $\pm$ 4		

SD, standard deviation; CTQ, Childhood Trauma Questionnaire; IDSSR, Inventory of Depressive Symptomatology Self-Report; STAI, State-Trait Anxiety Inventory.

^aParticipants endorsing at least moderate scores in CTQ categories.

^bDerived from CTQ categories, where ELS severity is indicated by “none/minimal”= 0, “low to moderate”= 1, “moderate to severe”= 2, or “severe to extreme”= 3, with a total range of 0–15

Table 2

Regions with Significant Group Differences in Regional Homogeneity

Region	BA	Coordinates (X, Y, Z)	Cluster Size	t-value	P-value
Right IPL	40	59, -31, 29	13	-4.36	< .001
Right STG	39	47, -49, 11	9	-4.87	.010

Abbreviations: IPL, inferior parietal lobule; STG, superior temporal gyrus; BA, Brodmann area. P-value, ClusterSim-corrected P-value. Coordinates based on the atlas of Talairach and Tournoux.

Table 3
Regions with Significant Group Differences in Resting State Functional Connectivity

Region	BA	Coordinates (X, Y, Z)	Cluster Size	Controls ^a	EL _S ^a	P-value
R precuneus	31	11, -31, 41	11	11.86	4.86	.005
L declive		-1, -67, -16	10	8.60	1.75	.005
L caudate		-16, 20, -7	8	4.48	-0.08	.050
L fusiform	18	-22, -85, -13	13	6.62	1.12	< .001

^a Z-scores of connectivity

Abbreviations: BA, Brodmann area; R, right; L, left; P-value, ClusterSim-corrected P-value. Coordinates based on the atlas of Talairach and Tournoux.