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Early life stress impacts dorsolateral prefrontal cortex functional connectivity in healthy adults: informing future studies of antidepressant treatments

Noah S. Philip^{a,*}, Thomas R. Valentine^a, Lawrence H. Sweet^b, Audrey R. Tyrka^a, Lawrence H. Price^a, and Linda L. Carpenter^a

^aLaboratory for Clinical and Translational Neuroscience, Butler Hospital, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University

^bClinical Neuroscience Laboratory, Department of Psychology, University of Georgia, Athens, GA

Abstract

Exposure to early life stress (ELS) is strongly associated with poor treatment outcomes, particularly for trauma-associated disorders such as depression. Little research to date, however, has examined the potential effects of ELS on outcomes with newer treatments, such as repetitive transcranial magnetic stimulation (rTMS). This study evaluated whether ELS exposure impacts resting state functional connectivity associated with brain regions targeted by rTMS. Twenty-seven medication-free adults without psychiatric or medical illness (14 with a history of at least moderate ELS) were scanned using a 3T magnetic resonance imaging (MRI) scanner during two 4-minute rest periods. The primary targets of rTMS, the left and right dorsolateral prefrontal cortex (DLPFC), were utilized as seed regions in connectivity analyses. Relative to controls, when seeding the left DLPFC, ELS subjects demonstrated significantly increased local connectivity with the left middle frontal gyrus and negative connectivity with the left precuneus. ELS status was also associated with negative connectivity from the right DLPFC to the left precuneus and left inferior parietal lobule. These findings demonstrate greater dissociation between the executive and default mode networks in individuals with a history of ELS, and these results may inform neuroimaging assessments in future rTMS studies of ELS-related conditions.

*Address correspondence to Noah S. Philip, M.D., Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906. Noah_Philip@Brown.edu.

CONTRIBUTORS

Dr. Philip designed the study, wrote the protocol and wrote the manuscript. Mr. Valentine drafted the manuscript, managed the literature searches and managed 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.

CONFLICT OF INTEREST

The authors identify no conflicts of interest. In the last three years, Dr. Philip has received research support from the Veterans Administration, Rhode Island Foundation, Neuronetics, Inc. and NeoSync, Inc. Dr. Price has received research support from Medtronic, Neuronetics, NIH, HRSA, and Neosync; he has served on advisory panels for Abbott and AstraZeneca; and he has served as a consultant to Gerson Lehrman, Wiley, Springer, Qatar National Research Fund, and Abbott. Dr. Tyrka has received research support from Medtronic, Neuronetics, NIH, and Neosync, and received an honorarium from Lundbeck. Dr. Carpenter has received research support from Medtronic, Neuronetics, NIH, and Neosync; she has served on advisory panels or provided consultant services for Abbott, AstraZeneca, Corcept, Johnson&Johnson and Takeda-Lundbeck. Dr. Sweet and Mr. Valentine report no conflicts of interest.

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Keywords

Early life stress; repetitive transcranial magnetic stimulation; dorsolateral prefrontal cortex; default mode network; functional connectivity; functional magnetic resonance imaging

1. Introduction

1.1. Early life stress

Exposure to early life stress (ELS), often defined as childhood maltreatment, abuse, and neglect, is a significant risk factor for the development of psychiatric disorders, such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) (Heim & Nemeroff, 2001). Such exposure is generally associated with poor outcomes, including increased resistance to pharmacologic treatment (Heim et al., 2010; Tyrka et al., 2013). ELS is highly prevalent, with reports indicating that over 6 million children in the United States are abused or neglected every year (U.S. Department of Health and Human Services, 2007), and it is probably even more prevalent in psychiatric populations (Pietrek et al., 2012).

1.2. ELS and rTMS

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive therapy approved for the treatment of MDD, with evidence supporting its use in several other psychiatric conditions (Slotema et al., 2010). rTMS for depression most commonly targets the left dorsolateral prefrontal cortex (left DLPFC), as a modulatory cortical region of the emotional network affected by that disorder (Mayberg, 2007); other studies have investigated right-sided rTMS (i.e., to the right DLPFC) for PTSD (e.g., Watts et al., 2012). Despite the prevalence of ELS in both of these conditions, little research to date has evaluated the potential impact of ELS on rTMS treatment parameters or outcomes.

1.3. rTMS outcomes

While the majority of meta-analyses examining the efficacy of rTMS support its antidepressant effects (Hovington et al., 2013), variability has been reported in treatment outcomes. A number of studies have sought to explain this variability by identifying patient-related factors that might predict the degree of improvement. For example, in a sham-controlled rTMS study, Holtzheimer et al. (2004) found that the duration of the current depressive episode predicted poorer treatment outcomes. Similarly, Fregni et al. (2006) evaluated data from six previous rTMS clinical trials for depression and found that older age and number of previously failed antidepressant trials were associated with a lack of improvement with rTMS. Lisanby et al. (2009) subsequently confirmed the results of these studies, demonstrating that rTMS outcomes were related to prior treatment resistance and duration of current depressive episode.

1.4. rTMS and neuroimaging

Recent neuroimaging studies have provided additional evidence of patient-related factors predictive of rTMS treatment outcomes. Kito et al. (2012) assessed cerebral blood flow in 24 patients with MDD prior to administration of rTMS. The authors found that the ratio of cerebral blood flow from the DLPFC to the medial prefrontal cortex (MPFC) was associated with treatment response, with a lower DLPFC/MPFC cerebral blood flow ratio predicting better outcomes. Dumas et al. (2012) recently examined the effects of rTMS on health-related quality of life in individuals with MDD and assessed associated changes in regional cerebral blood flow. They found that improvement in social and mental health following rTMS was correlated with concomitant decreased perfusion of the precuneus, a region of the default mode network (DMN).

A common factor in each of these studies is the relationship between rTMS outcomes, the DLPFC, and regions involved in the DMN. The DMN is a series of brain regions, including the medial prefrontal cortex (MPFC), posterior cingulate cortex/precuneus (PCC), and middle temporal regions, which are active when an individual is in a resting state (Greicius et al., 2003). The DMN is believed to be involved in introspection and self-monitoring (Fransson, 2006), and previous studies suggest that the DMN may be linked to a variety of psychiatric disorders through stress exposure, manifest as diminished resting state functional connectivity (RSFC) (Bluhm et al., 2009; Cisler et al., 2012; Lanius et al., 2010; Philip et al., 2013a; Zhu et al., 2012).

1.5. The DLPFC and ELS

A growing body of evidence suggests that the structure and function of the DLPFC, the primary target of rTMS, can be affected by ELS. Several volumetric studies have found decreased DLPFC grey matter in ELS participants (Cohen et al., 2006; Hanson et al., 2010; Tomoda et al., 2009), and functional imaging studies have supported these findings. Raine et al. (2001) found reduced activity of the DLPFC in ELS-exposed participants during a working memory challenge, while Carrion et al. (2008) found decreased DLPFC activation in ELS participants during a Go/No-Go task. Older functional studies using positron emission tomography (PET) have demonstrated altered DLPFC activity during traumatic script-driven imagery (Bremner et al., 1999; Schmahl et al., 2004; Shin et al., 1999). More recently, Cisler et al. (2012) found that in individuals with a history of trauma exposure and current or past depression, DLPFC connectivity was generally reduced, and this reduction was associated with greater ELS severity.

1.6. Summary and study objectives

In summary, previous studies have demonstrated that ELS exposure is associated with multiple neuroimaging findings relevant to rTMS, principally involving the DMN, and that ELS exposure also impacts the DLPFC. Since the DMN and executive network, including the DLPFC, are “anticorrelated” (Buckner et al., 2008; Fox et al., 2005), the relationship between these two networks might be a useful metric to evaluate neuroimaging effects of rTMS. Importantly, DLPFC activity can be affected by multiple antidepressant treatments, including rTMS, selective serotonin reuptake inhibitors (e.g., fluoxetine, escitalopram) and multiple reuptake inhibitors such as venlafaxine (for a review, see Delaveau et al., 2011). Since rTMS is unique in its ability among available treatments to specifically target the DLPFC, investigating DLPFC-associated connectivity may generate important information to inform future rTMS studies. This study evaluated whether ELS impacts RSFC associated with the targets of rTMS, to uncover potential neuroimaging correlates of ELS that might subsequently inform future studies integrating RSFC and rTMS in ELS-related psychiatric conditions. We hypothesized that ELS exposure would be associated with greater dissociation between the DLPFC and the DMN, and that this disruption would be associated with ELS severity.

2. Methods

2.1. Participants

Participants with a reported history of ELS exposure ($n = 14$) and healthy controls ($n = 13$) were recruited from an ongoing longitudinal study examining potential endophenotypes for mood/anxiety disorders; this group represents an expanded sample from previously reported data that demonstrated decreased DMN functional connectivity in individuals with a history of ELS (Philip et al., 2013a). The current study adds to these previous findings by investigating the effects of ELS on functional connectivity in multiple brain networks, via selection of seed regions whose function may have more direct implications for treatment.

Brown University and Butler Hospital Institutional Review Boards approved all study protocols, and all protocols were conducted in accordance with the latest version of the Declaration of Helsinki. All participants provided informed consent following full explanation of study procedures. Participants were reimbursed \$50 for their participation.

Study inclusion criteria were 1) a report of physical, emotional, or sexual abuse as a child, defined as a Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998) subscale classification score of “moderate/severe” or “severe/extreme” (ELS group), or absence of such history confirmed with the same instrument for the control group, and 2) absence of a current DSM-IV-TR Axis I or Axis II psychiatric disorder, assessed by the Structured Clinical Interview for DSM-IV-TR (SCID and SCID II) (First et al., 1994). ELS and control participants were matched on age and gender. Exclusion criteria were contraindications to MRI scanning (such as bodily inclusion of ferromagnetic objects), current treatment with any psychotropic medications, and active medical illness (assessed by medical history, physical and neurological examinations, 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 also 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 (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; acquisition parameters were TR = 1900 ms, TE = 2.98 ms, and FOV 256 mm². Resting state images were acquired during two separate 4-minute epochs, during which participants were instructed to remain awake and watch a white fixation cross against a black background. 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 a total of 192 whole brain volumes with spatial resolution of 3 mm³ per voxel.

2.3. Preprocessing

After image acquisition, anatomic data were transformed to standard Talairach stereotaxic space (Talairach & Tournoux, 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 analyses. Bandpass filtering was performed at .009 sec < f < 0.08 sec to reduce the effect of high-frequency noise and low-frequency drift. Nuisance variables for each voxel included average ventricle and white matter time series, with the six-parameter estimates of head motion (utilizing both demeaned and derivative values). The predicted time course of these nuisance variables was then subtracted from the full voxel time series to yield a residual time series to be used in later correlation analyses. Global signal regression was not implemented due to the growing concern that this preprocessing step may spuriously influence correlations in resting state data (Fox & Greicius, 2010; Murphy et al., 2009; Saad et al., 2012). Subsequent steps included normalization of within-run intensity and blurring to a 6-mm full width at half maximum Gaussian distribution. All preprocessing and subsequent data analyses utilized the Analysis of Functional NeuroImages (AFNI) (Cox, 1996) software unless otherwise specified.

2.4. Head motion analysis

Reflecting the growing concern regarding the impact of participant motion in resting state MRI studies (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012), we

undertook several measures to ensure our final results were not confounded by motion. First, during individual subject analyses, any TR with motion greater than 1.5 mm was removed; the selection of this threshold was informed by results from Posner et al. (2013). Second, we designated motion in the x, y, and z directions and roll, pitch, and yaw, generated during individual alignment and registration, as regressors of no interest during preprocessing, prior to blurring. Lastly, we compared group differences in head motion; for this comparison we used the derivative of the Euclidean norm of motion to combine translational movement (in millimeters) with rotational movements (in degrees), using the assumption that 1 degree roughly equaled 1 mm. Group motion was evaluated using analysis of variance (ANOVA), with significance set at two-tailed $p < .05$, using SPSS Statistics 20 (IBM Corporation, Armonk, NY).

2.5. Seed selection and functional connectivity analysis

We utilized resting state seed-based connectivity analysis (SCA) to identify differences between ELS and non-exposed groups. This method is a robust analytic approach to identify resting state networks (Biswal et al., 2010; Cole et al., 2010; Smith et al., 2010), although its principal limitation is potential misplacement of origin seeds. Since we were interested in characterization of ELS correlates that would be relevant to future studies of rTMS in traumatized populations, we used a seed that reflected the most commonly used rTMS targets, the left and right DLPFC. This study implemented methods adapted from Fox et al. (2012) which showed that functional connectivity between the subgenual anterior cingulate and DLPFC was a critical determinant of rTMS efficacy. In brief, this study showed that the ideal location for the rTMS coil was in the overlap of Brodmann Areas 46 and 9, in approximately a 25-mm area, at Talairach coordinates 32, 33, 24 and -33, -33, 24 for the L and R DLPFC, respectively. To generate individually meaningful results, these bilateral seed regions were combined with an individual's segmented cortical ribbon, generated separately using the FMRI module of SPM 9 (Functional Imaging Laboratory, University College London, London, UK), at a probability of at least 75%. Average time series data were extracted from this mask and used in subsequent analyses, which utilized voxel-based general linear modeling (GLM) to quantify the relationship between the DLPFC seeds 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). The individual maps of Z values representing the strength of the DLPFC BOLD time-series relationship to each voxel in the cortical ribbon served as the basic measure to generate SCA maps. 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 for imaging data was set at $p < .05$, utilizing family-wise error (FWE) multiple comparisons correction. FWE correction was implemented using AFNI's ClusterSim program, which uses Monte Carlo simulations to determine required voxel and cluster size for a predetermined alpha level in a given matrix size (3dClustSim -fwhmxyz 5.29 5.39 5.25 -dxyz 3 3 3 -nxyz 54 64 50). Other planned comparisons included correlations between Z-scores of connectivity with ELS type and severity, as well as with anxiety and depression rating scales. Anxiety symptoms were assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), while depressive symptoms were assessed using the Inventory of Depressive Symptomatology Self-Report (IDSSR) (Rush et al., 1986). Statistical thresholds for these comparisons were set at a two-tailed $p < .05$, using SPSS.

3. Results

3.1. Participants and head motion analysis

Demographic characteristics are reported in Table 1. There were no significant differences between groups in age, gender, or education. 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. Connectivity analyses

The spatial distribution of resting state functional connectivity with the seed regions is summarized in Table 2 (left DLPFC seed) and Table 3 (right DLPFC seed). ELS subjects, compared to the reference control group, demonstrated significantly positive localized left DLPFC RSFC with the left middle frontal gyrus ($p_{\text{corrected}} < .001$) and significantly negative RSFC between the left DLPFC and left precuneus ($p_{\text{corrected}} = .01$) (Table 4a; Figure 1). ELS subjects also exhibited significantly negative connectivity from the right DLPFC to the left precuneus ($p_{\text{corrected}} < .001$) and negative RSFC with the left inferior parietal lobule (IPL) ($p_{\text{corrected}} = .05$) (Table 4b; Figure 2). Average Z-scores and directions of effect in regions showing significant group differences are reported in Tables 4a and 4b. The sign of Z-scores (positive or negative) for all regions examined were in the opposite direction for the ELS group, compared to controls.

3.3. Correlations between Z-scores of connectivity and rating scales

There was a significant positive correlation between left DLPFC/left middle frontal gyrus connectivity strength and ELS severity ($r = .58$, $p < .01$), and left DLPFC/left precuneus connectivity was negatively correlated with ELS severity ($r = -.49$, $p < .01$). The strength of right DLPFC/left precuneus and right DLPFC/left IPL connectivity was also negatively correlated with ELS severity ($r = -.65$, $p < .01$ and $r = -.53$, $p < .01$, for the precuneus and IPL, respectively).

Within the ELS group, there was a trend for negative correlation between ELS severity and right DLPFC/left precuneus connectivity ($r = -.51$, $p = .06$); analyses of correlations between RSFC and specific ELS subtypes revealed a significant negative correlation between right DLPFC/left precuneus connectivity and emotional abuse ($r = -.66$, $p = .01$) and trend-level findings for emotional neglect ($r = -.52$, $p = .058$).

Comparison of group IDSSR scores revealed a significantly higher mean score for ELS participants (10 ± 6 vs. 3 ± 2 , for ELS and non-ELS, respectively, $p < .01$), consistent with nonclinical depressive symptoms (Rush et al., 1986). IDSSR scores were not significantly correlated with RSFC from the seed regions ($p > .1$). While there were no significant group differences in state anxiety ($p > .1$), the ELS group exhibited significantly higher trait anxiety (33 ± 9 vs. 26 ± 5 , for ELS and non-ELS, respectively, $p = .04$). STAI scores for both the ELS and control groups were below those considered indicative of clinically significant symptoms (Spielberger et al., 1983). There were no significant correlations between STAI scores and connectivity ($p > .1$).

4. Discussion

In this study, we investigated patterns of RSFC from a clinically relevant seed of the executive network, and compared ELS-exposed individuals to those without this exposure. To our knowledge this is the first study in this population investigating changes in RSFC using this seed selection for connectivity. Overall, this study found that ELS exposure, in the absence of formal psychiatric disorders or medication use, is correlated with dissociation

between executive and default mode networks, concurrent with increased localized connectivity.

4.1. Within-group results

Within-group findings from this study are generally consistent with existing models of executive network functional connectivity, such as positive connectivity between the DLPFC, medial frontal gyrus, and insula (Fox & Raichle, 2007; Fox et al., 2005; Spreng et al., 2009; Toro et al., 2008). These results indicate the validity of DLPFC seed placement. Although there is little data evaluating RSFC in trauma-exposed, diagnosis-free individuals, these results are similar to findings from Ye et al. (2012) demonstrating decreased RSFC between the right DLPFC and parietal lobe in an MDD sample. This similarity is further supported by the increased depressive symptoms in our ELS-exposed group, although this should be interpreted with caution since IDSSR values were generally below those considered clinically significant.

4.2. Negative DLPFC to left precuneus connectivity

These findings also demonstrated negative connectivity between principal regions of the executive and default mode networks (i.e., bilateral DLPFC to left precuneus). These two networks are often considered “anticorrelated,” as activity in one network generally increases while the other decreases (Buckner et al., 2008; Fox et al., 2005). While different from activity, these findings suggest an exaggerated anticorrelation between these two networks, with relatively larger effects on the right compared to the left. This is supported by the opposite direction of RSFC (i.e., negative Z-score of connectivity) found in the ELS group. These results are consistent with the hypothesis that symptoms of trauma-related disorders are associated with an inability to appropriately shift between networks, such as the state of being stuck in default mode function, as manifested, for example, by rumination in depression (Li et al., 2013; Pizzagalli, 2011; Zhu et al., 2012) or impaired self-referential processing and dissociation in PTSD (Bluhm et al., 2009). Precuneus activity is also related to response to rTMS treatment: Dumas et al. (2012) showed that improvements in quality of life in depression after rTMS were associated with a decrease in precuneus activity. This suggests that rTMS stimulation of the DLPFC results in increased synchrony (i.e., resolution of decreased connectivity) between the DLPFC and precuneus, and that disrupted connectivity could be studied as a potential biomarker of rTMS response.

4.3. Negative right DLPFC to left IPL connectivity

Compared to the non-exposed group, ELS participants showed several novel findings, including negative right DLPFC to left IPL connectivity. The IPL is thought to be involved in spatial memory and visual-spatial processing (Pardo et al., 1991; Petersen et al., 1988; Posner et al., 1988), and is one of the last brain regions to mature, which may make it more susceptible to neurotoxic effects of prolonged glucocorticoid secretion associated with traumatic exposure (Conrad et al., 2007; Patel & Finch, 2002). Our findings, that decreased right DLPFC/IPL connectivity correlates with emotional abuse/neglect, support this hypothesis. That emotional abuse and neglect contribute more than other forms of maltreatment might be due to the greater tendency for this type of maltreatment to be chronic. These results are also consistent with previous results in this sample that showed diminished resting state activity in the IPL (Philip et al., 2013b), suggesting that both localized activity and more distant connectivity are impaired in this region. The IPL is also described as part of the cortical mirror neuron system (Ocampo et al., 2011), and decreased DLPFC/IPL connectivity may indicate ELS is associated with impaired regulation of this network. Importantly, both the IPL and DLPFC are involved in network pathology associated with depression (Delaveau et al., 2011), and as such, these results suggest that

ELS exposure can contribute to decreased patterns of connectivity associated with this disorder.

4.4. Positive left DLPFC local connectivity

Interestingly, this study also found positive local connectivity when seeding the left DLPFC. To our knowledge, this is the first study to demonstrate this finding, and as such should be considered preliminary until replicated. One explanation of these results is that ELS results in a relative disconnection of the left DLPFC or an increase in BOLD signal heterogeneity, both of which would result in an increase in localized connectivity compared to other brain regions. We hypothesize that this may be due to a reallocation of cognitive resources towards internal stimuli, similar to that seen in rumination in depression, which would in turn reduce DLPFC activity and impact connectivity (Hamilton et al., 2011). Another interpretation is that our empirically generated seed region did not sufficiently include all areas of a functionally defined DLPFC. This would support the hypothesis that functional, rather than anatomical, definition of rTMS targeting may be a fruitful area for future research.

4.5. Direction of effects

All RSFC findings in the ELS group were in the opposite direction (i.e., reversed sign), compared to our reference control group. These results were consistent across all regions showing significant group-level differences. Z-scores representing connectivity between hubs of the executive and default mode networks were almost identical in magnitude yet opposite in direction. This inverse pattern of RSFC further suggests that ELS results in increased anticorrelation between these networks even in the absence of task. We hypothesize that the positive association between localized DLPFC regions represents increased synchronous activity of local neuronal populations or concurrent desynchronization with distal regions. We interpret change in connectivity between the right DLPFC to left IPL to be a simple attenuation in connectivity (rather than an anticorrelation), as the mean Z-score of -0.01 in the ELS group was not significant on its own and has an effect size very close to zero.

4.5. Limitations

The principal limitation of this study is that it did not include a clinically ill comparison group, which would typically be the recipient of TMS therapy. While this omission was deliberate (i.e., to examine the unique neuroimaging correlates of stress exposure without the potentially confounding influence of medication or other factors), it limits the generalizability of the findings to patients. The sample size of the current study was also relatively small, so findings from this report should be interpreted as preliminary. Additionally, since this investigation was cross-sectional, it is possible that some of the participants imaged will develop trauma-related disorders in the future. Another limitation of the study is potential inaccuracies inherent in self-reports of ELS, although this is a limiting factor in all cross-sectional studies utilizing retrospective reports of trauma exposure.

4.6. Summary

In summary, we found that ELS is associated with increased localized connectivity and diminished connectivity between traditional clinical rTMS targets and a DMN region implicated in clinically relevant rTMS outcomes. These results confirm previous findings of dissociation between executive and default mode networks in association with early stress, and may be useful for future work aimed at refining rTMS targets and parameters in patients with stress-related disorders.

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Figure 1.

Group Differences (Early Life Stress vs. Non-Exposed Controls) in Left DLPFC Seed Connectivity

Sagittal images showing regions with significant group differences in resting state functional connectivity from the left dorsolateral prefrontal cortex seed region, comparing early life stress (ELS) vs. non-exposed controls. Results from independent samples *t*-test are thresholded at family-wise error corrected $p < .05$; yellow indicates positive Z scores of connectivity, while blue indicates negative scores. X coordinates of each slice are shown at the bottom left of the corresponding image. A) left middle frontal gyrus, B) left precuneus.

Figure 2.

Group Differences (Early Life Stress vs. Non-Exposed Controls) in Right DLPFC Seed Connectivity

Sagittal images showing regions with significant decreased resting state functional connectivity from the right dorsolateral prefrontal cortex seed region, comparing early life stress (ELS) vs. non-exposed controls. Results from independent samples *t*-test are thresholded at family-wise error corrected $p < .05$; blue indicates negative Z scores of connectivity. X coordinates of each slice are shown at the bottom left of the corresponding image. A) left precuneus, B) left inferior parietal lobule.

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	ns
Gender (<i>n</i> , % Female)	7 (58)	9 (69)	ns
College Education (%)	64	50	ns
CTQ			
Category (<i>n</i> , %) ^{<i>a</i>}			
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>) ^{<i>b</i>}	7 $\pm$ 4		

SD, standard deviation; CTQ, Childhood Trauma Questionnaire.

^{*a*}Participants endorsing at least moderate scores in CTQ categories.

^{*b*}Sum of severity scores for the five 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
Spatial Distribution of Resting State Functional Connectivity from the Left DLPFC Seed

2a. ELS Group					
Region	BA	Coordinates (x,y,z)	Cluster Size	t-score	p-value
R Middle Frontal Gyrus	10	38, 53, 2	172	5.8	<.001
L Middle Frontal Gyrus	7	37, 47, 14	138	6.6	<.001
R Inferior Parietal Lobule	40	53, -40, 38	87	5.3	<.001
L Precentral Gyrus	6	-40, 2, 29	65	3.5	<.001
L Inferior Parietal Lobule	40	-49, -52, 44	52	5.5	<.001
L Insula	13	-28, 17, 5	37	5.7	<.05

2b. Non-ELS Group					
Region	BA	Coordinates (x,y,z)	Cluster Size	t-score	p-value
R Middle/Inferior Frontal Gyrus	9	47, 11, 32	105	7.2	<.001
R Inferior Parietal Lobule	40	53, -43, 47	73	4.9	<.001
R Middle Frontal Gyrus	10	41, 41, 17	42	3.3	.025
R Uvula (Cerebellum)	n/a	32, -76, -25	38	-3.5	.050

Abbreviations: BA, Brodmann Area. p-value, ClusterSim-corrected p-value. L, left. R, right. Coordinates based in the atlas of Talairach and Tournoux.

Table 3
Spatial Distribution of Resting State Functional Connectivity from the Right DLPFC Seed

3a. ELS Group					
Region	BA	Coordinates (x,y,z)	Cluster Size	t-score	p-value
R Lingual Gyrus	18	11, -82, -13	152	-7.2	< .001
L Inferior Frontal Gyrus	46	-40, 41, 5	94	4.7	< .001
R Declive (Cerebellum)	n/a	41, -76, -19	82	-4.1	< .001
L Middle Frontal Gyrus	9	-46, 20, 32	43	4.0	.010
R Middle Frontal Gyrus	10	32, 44, 8	39	4.5	.025
L Insula	13	-25, 20, 8	38	4.8	.050

3b. Non-ELS Group					
Region	BA	Coordinates (x,y,z)	Cluster Size	t-score	p-value
L Middle Frontal Gyrus	46	-43, 35, 23	72	5.9	< .001
L Insula	13	-31, 20, 2	36	5.4	.050

Abbreviations: BA, Brodmann Area. p-value, ClusterSim-corrected p-value. L, left. R, right. Coordinates based in the atlas of Talairach and Tournoux.

Regions Showing Significant Group Differences (Early Life Stress vs. Non-Exposed Controls) in Resting State Functional Connectivity from Seeded Regions

Table 4

4a. Left DLPFC Seed						
Region	BA	Coordinates (x,y,z)	Cluster Size	Z-score		p-value
				ELS	Control	
L MFG	8	-46, 14, 38	57	.12	-.04	5.34 < .001
L Precuneus	7	-10, -52, 62	45	-.06	.07	-4.18 .010

4b. Right DLPFC Seed						
Region	BA	Coordinates (x,y,z)	Cluster Size	Z-score		p-value
				ELS	Control	
L Precuneus	7	-13, -55, 59	90	-.05	.04	-4.12 < .001
L IPL	40	-34, -43, 44	37	-.01	.05	-4.16 .05

Abbreviations: BA, Brodmann Area. Z-score, mean Z-score of connectivity. Control, non-exposed controls. p-value, ClusterSim-corrected p-value. L, left. R, right. MFG, middle frontal gyrus. Coordinates based in the atlas of Talairach and Tournoux.

Abbreviations: BA, Brodmann Area. p-value, ClusterSim-corrected p-value. Z-score, mean Z-score of connectivity. Control, non-exposed controls. L, left. R, right. IPL, inferior parietal lobule. Coordinates based in the atlas of Talairach and Tournoux.