Journal of Psychiatric Research 52 (2014) 63–69

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

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], Linda L. Carpenter [a]

[a] Laboratory for Clinical and Translational Neuroscience, Butler Hospital, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, 345 Blackstone Boulevard, Providence, RI 02906, USA
[b] Clinical Neuroscience Laboratory, Department of Psychology, University of Georgia, Athens, GA, USA

ARTICLE INFO

Article history:
Received 22 August 2013
Received in revised form
13 January 2014
Accepted 16 January 2014

Keywords:
Early life stress
Repetitive transcranial magnetic stimulation
Dorsolateral prefrontal cortex
Default mode network
Functional connectivity
Functional magnetic resonance imaging

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-min 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.

Published by Elsevier Ltd.

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 and 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

* Corresponding author.
E-mail address: Noah_Philip@Brown.edu (N.S. Philip).

0022-3956/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jpsychires.2014.01.014

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 gray 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 and 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 mm^3) T1 images were acquired for anatomic reference; acquisition parameters were TR = 1900 ms, TE = 2.98 ms, and FOV 256 mm^2. Resting state