Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Effects of acute tryptophan depletion on raphé functional connectivity in depression

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ARTICLE INFO

Article history:
Received 30 August 2014
Received in revised form
21 July 2015
Accepted 31 August 2015

Keywords:
SSRI antidepressant
Serotonin
fMRI
Frequency
Thalamus
Anterior cingulate

ABSTRACT

Depression remains a great societal burden and a major treatment challenge. Most antidepressant medications target serotonergic raphé nuclei. Acute tryptophan depletion (ATD) modulates serotonin function. To better understand the raphé's role in mood networks, we studied raphé functional connectivity in depression. Fifteen depressed patients were treated with sertraline for 12 weeks and scanned during ATD and sham conditions. Based on our previous findings in a separate cohort, resting state MRI functional connectivity between raphé and other depression-related regions (ROIs) was analyzed in narrow frequency bands. ATD decreased raphé functional connectivity with the bilateral thalamus within 0.025–0.05 Hz, and also decreased raphé functional connectivity with the right pregenual anterior cingulate cortex within 0.05–0.1 Hz. Using the control broadband filter 0.01–0.1 Hz, no significant differences in raphé-ROI functional connectivity were observed. Post-hoc analysis by remission status suggested increased raphé functional connectivity with left pregenual anterior cingulate cortex in remitters ($n=10$) and decreased raphé functional connectivity with left thalamus in non-remitters ($n=5$), both within 0.025–0.05 Hz. Reducing serotonin function appears to alter coordination of these mood-related networks in specific, low frequency ranges. For examination of effects of reduced serotonin function on mood-related networks, specific low frequency BOLD fMRI signals can identify regions implicated in neural circuitry and may enable clinically-relevant interpretation of functional connectivity measures. The biological significance of these low frequency signals detected in the raphé merits further study.

1. Introduction

Depression remains a great societal burden and a major treatment challenge. Depression and suicide are associated with altered serotonin function (Maes et al., 1995; Delgado et al., 1999; Engstrom et al., 1999; Caspi et al., 2003; Bach-Mizrachi et al., 2006, 2008; Meyer, 2007). Altered serotonergic markers in depression and suicide have been identified specifically in the raphé nuclei (Bach-Mizrachi et al., 2006, 2008). Serotonin and the raphé are targets of most antidepressant medications (Scuvee-Moreau and Dresse, 1979; Blier and El Mansari, 2013).

Depression and its treatments are also associated with altered functional connectivity across multiple neural networks (Greicius et al., 2007; Fales et al., 2009; Sheline et al., 2010; Wang et al., 2012; Zhu et al., 2012; Li et al., 2013; Posner et al., 2013), but have not been linked to regions associated with specific neurotransmitter function. Changes in functional connectivity of the raphé during tryptophan depletion were recently reported (Salomon et al., 2011) and may be a promising biomarker for depression. Further exploration of this proxy measure of serotonergic activity is needed.

Functional magnetic resonance imaging (fMRI) connectivity metrics depend on specific frequencies of blood oxygen level dependent (BOLD) activation and anatomical projections between

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http://dx.doi.org/10.1016/j.pscychresns.2015.08.015
0925-4927/

the involved regions. While the BOLD fMRI signal does not directly measure neural behavior, it has been correlated with measures of neural activity at specific frequencies (Logothetis and Wandell, 2004; Scholvinck et al., 2010; Magri et al., 2012). Frequencies of BOLD activation in the raphé may be influenced by raphé neuron activity. Spontaneous firing rates of neurons in the raphé occur within a range of 0.5–2.5 Hz (Aghajanian et al., 1978), which overlaps with frequencies detectable by fMRI. Raphé stimulation at low (0.5 Hz) frequencies produces an increase in serotonin release, differing markedly from higher frequency (10 Hz) stimulation which is associated with decreases in release (Sheard and Aghajanian, 1968). Further, models of depression are associated with changes in raphé firing rates at low (0.2 Hz) frequencies (Yavari et al., 1993). Low (0.3 Hz) frequency activity in the raphé also appears to be related to antidepressant effects (Sheard et al., 1972). Local firing rate adjustments during serotonin-reuptake inhibitor (SRI) treatments, such as sertraline, coincide with mood response (Blier et al., 1987; de Montigny et al., 1990; Chaput et al., 1991; Blier and de Montigny, 1994; Owens, 1996; Evans et al., 2008). Together this evidence indicates that patterns of neuronal activity within the raphé relates significantly to depressive symptomatology and response to treatment.

Differential functional coupling of the raphé with extra-raphé regions likely relies on neuronal projections of the serotonin network, since the other neurons in the raphé are local interneurons. Serotonergic neurons from the brainstem pontomesencephalic raphé (which we will refer to here as dorsal raphé) project broadly to limbic cortical and other regions, including the thalamus (Baker et al., 1990, 1991a; Jacobs and Azmitia, 1992). Reciprocally, feedback from cortical regions, including the medial prefrontal cortex and subgenual anterior cingulate cortex, provides rapid and reversible effects on serotonergic neuronal function in the raphé (Amat et al., 2005; Gabbott et al., 2005; Warden et al., 2012). These anatomical and functional relationships with the raphé predict a role for raphé connectivity using fMRI connectivity approaches.

To test for changes in raphé functional connectivity with mood-related regions, a challenge paradigm is useful. Modulation of serotonin precursor availability by acute tryptophan depletion (ATD) decreases serotonin synthesis in the raphé and has been associated with worsening mood (Delgado et al., 1990). ATD alters intra-raphé activation frequencies and raphé-to-other-region functional connectivity (Salomon et al., 2011).

In the present study, MRI functional connectivity was analyzed in narrow frequency ranges comparable to those used in the prior study, but using a new, prospectively sertraline-treated, depressed cohort. Based on findings from the prior study, we hypothesized that raphé-to-ROI functional connectivity would decrease with reduced serotonin availability during ATD. As in the prior study of connectivity with the dorsal raphé, we selected brain regions (ROIs) implicated in the pathophysiology of depression or known to be rich in serotonergic innervation.

2. Methods

This study of ATD effects on raphé activation was designed with considerable caution regarding the reliability of changes in fMRI signal in a region putatively identified as anatomically consistent with dorsal raphé, with full awareness and many precautions to limit the risk that nearby tissues might be involved.

2.1. Design and sample

An institution-wide email solicited depressed adults, age 18–50, who were medication-free for at least 4 weeks. A current DSM-IV-TR diagnosis of major depressive disorder was determined by clinical interview and confirmed with a structured diagnostic interview using the Mini International Neuropsychiatric Interview, MINI (Sheehan et al., 1998). Included participants also scored 18 or higher on the 17-item Hamilton rating scale for depression (HAM-D) (Hamilton, 1960) and remission was defined as post-sertraline treatment HAM-D score less than eight.

Participants were excluded for other current primary psychiatric diagnosis, current or prior need for inpatient management, sertraline failure or documented treatment-resistance, substance use within 1 month, daily nicotine use, pregnancy or lactation, oral contraceptive use, migraine, hepatitis, endocrinopathy, or metal implants. All participants provided signed informed consent before beginning study procedure. The Vanderbilt Institutional Review Board approved this study.

All participants were treated with sertraline 50 mg daily for 1 week, then 100 mg for 11 weeks. Participants were allowed 0.5 mg lorazepam for 3 doses in the first week of sertraline. Beyond the first week, all participants were restricted to sertraline monotherapy. Clinical visits occurred every 1–2 weeks during the treatment period. HAM-D assessments were completed at baseline and at each follow-up visit. After 12 weeks of treatment, each subject participated in two random-sequence, double-blind test days that were one week apart. Each test day morning consisted of General Clinical Research Center admission, HAM-D mood rating, blood draw for plasma tryptophan concentration, and administration of either the sham or ATD diet. Randomization and blinding was performed by the Vanderbilt Investigational Drug Service, which prepared the amino acid mixtures for both diets. Active ATD amino acid (100 g, 'full-strength') mixtures contained 15 amino acids in the balance found in human milk, but without tryptophan, as detailed previously (Delgado et al., 1990; Salomon et al., 2011). Control diets were identical, but included L-tryptophan. Six hours later (at 3 pm), HAM-D mood rating and blood sampling were repeated, immediately prior to the 45–60-min MRI scan. Morning and afternoon mood ratings used all items from the HAM-D, with carry-forward of sleep and appetite items through the day. The participant was given a normal, tryptophan-rich meal after the conclusion of the scan, regardless of which diet was received. One week later, the test day procedure was repeated with the alternate diet (*i.e.* if the participant had first received the ATD diet, the procedure was repeated with the sham diet).

2.2. MRI acquisition

Imaging data were collected on a 3T Phillips Integra scanner. For each session the scan sequence included a 3D T1 anatomical (6.5 min, 1 mm^3 isotropic voxel size) and a 6.7 min resting-state BOLD scan (200 volumes, TR 2000 msec, TE 25 msec, 30 slices, 3.75×3.75 mm^2 in-plane resolution, 4.5 mm thick and 0.5 mm gap). For the resting-state scans, participants were instructed to lie still and close their eyes but stay awake.

2.3. Data analysis

2.3.1. Preprocessing

Structural and functional imaging data was preprocessed using SPM8 (Friston et al., 1994) toolbox for Matlab (MathWorks, Inc., Massachusetts, United States). For intra-subject comparability between sessions, a mean structural image was calculated for each subject across conditions prior to segmentation. We applied slice-timing and motion correction to each functional session. The mean functional image was then calculated and used to create a co-registration transform for each of the sessions' functional data to the mean structural image. Finally, for each subject, the structural, subject-specific raphé ROI, and functional volumes were all normalized to ICBM-152 MNI (Montreal Neurologic Institute)

Please cite this article as: Weinstein, J.J., et al., Effects of acute tryptophan depletion on raphé functional connectivity in depression. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.08.015