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

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Abnormal striatal resting-state functional connectivity in adolescents with obsessive–compulsive disorder

Gail A. Bernstein [a,*], Bryon A. Mueller [b], Melinda Westlund Schreiner [a], Sarah M. Campbell [a], Emily K. Regan [a], Peter M. Nelson [a,d], Alaa K. Houri [a], Susanne S. Lee [a], Alexandra D. Zagoloff [a], Kelvin O. Lim [b], Essa S. Yacoub [c], Kathryn R. Cullen [a]

[a] University of Minnesota, Division of Child and Adolescent Psychiatry, F282/2A West, 2450 Riverside Avenue, Minneapolis, MN 55454, USA
[b] University of Minnesota, Department of Psychiatry, F282/2A West, 2450 Riverside Avenue, Minneapolis, MN 55454, USA
[c] University of Minnesota, Center for Magnetic Resonance Research, 2021–6th Street SE, Minneapolis, MN 55455, USA
[d] Penn State College of Education, Department of Educational Psychology, Counseling, and Special Education, 106 Cedar Building, University Park, PA 16802, USA

ARTICLE INFO

Article history:
Received 6 April 2015
Received in revised form
9 October 2015
Accepted 16 November 2015

Keywords:
Functional MRI
Neuroimaging
Striatum
Insula
Operculum

ABSTRACT

Neuroimaging research has implicated abnormalities in cortico-striatal-thalamic-cortical (CSTC) circuitry in pediatric obsessive–compulsive disorder (OCD). In this study, resting-state functional magnetic resonance imaging (R-fMRI) was used to investigate functional connectivity in the CSTC circuitry in adolescents with OCD. Imaging was obtained with the Human Connectome Project (HCP) scanner using newly developed pulse sequences which allow for higher spatial and temporal resolution. Fifteen adolescents with OCD and 13 age- and gender-matched healthy controls (ages 12–19) underwent R-fMRI on the 3T HCP scanner. Twenty-four minutes of resting-state scans (two consecutive 12-min scans) were acquired. We investigated functional connectivity of the striatum using a seed-based, whole brain approach with anatomically-defined seeds placed in the bilateral caudate, putamen, and nucleus accumbens. Adolescents with OCD compared with controls exhibited significantly lower functional connectivity between the left putamen and a single cluster of right-sided cortical areas including parts of the orbitofrontal cortex, inferior frontal gyrus, insula, and operculum. Preliminary findings suggest that impaired striatal connectivity in adolescents with OCD in part falls within the predicted CSTC network, and also involves impaired connections between a key CSTC network region (i.e., putamen) and key regions in the salience network (i.e., insula/operculum). The relevance of impaired putamen-insula/operculum connectivity in OCD is discussed.

1. Introduction

Obsessive-compulsive disorder (OCD) is a debilitating disorder with a lifetime prevalence rate of approximately 2.7% (Ruscio et al., 2010; Kessler et al., 2012). Neuroimaging research has implicated cortico-striatal-thalamic cortical (CSTC) circuitry in OCD (Huyser et al., 2009). These networks connect neurons in the cortex, striatum (i.e., caudate, putamen, nucleus accumbens), thalamus, and back to the cortex (Alexander et al., 1986; Maia et al., 2008; Kalra and Swedo, 2009). Theory suggests that abnormalities in the CSTC circuitry result in the obsessions and compulsions of pediatric OCD (Kalra and Swedo, 2009). In addition to the CSTC network, other networks and brain regions appear to be involved in OCD (Menzies et al., 2008; Fitzgerald et al., 2010; Jang et al., 2010; Milad and Rauch, 2012).

Advances in neuroimaging that assess brain connectivity allow for a sophisticated understanding of neural networks. Resting-state functional magnetic resonance imaging (R-fMRI) assesses the spontaneous slow-wave fluctuations of blood-oxygen-level-dependent (BOLD) signals between brain areas at rest (Biswal et al., 1995). Functional connectivity is determined by inter-regional correlations of these temporal patterns (Fox and Raichle, 2007). There have been a number of resting-state studies of OCD (Harrison et al., 2009; Fitzgerald et al., 2010, 2011; Jang et al., 2010;

* Corresponding author.
E-mail addresses: berns001@umn.edu (G.A. Bernstein), muell093@umn.edu (B.A. Mueller), westl110@umn.edu (M.W. Schreiner), campb767@umn.edu (S.M. Campbell), rega0148@umn.edu (E.K. Regan), pmn12@psu.edu (P.M. Nelson), houri005@umn.edu (A.K. Houri), leexx310@umn.edu (S.S. Lee), zagol001@umn.edu (A.D. Zagoloff), kolim@umn.edu (K.O. Lim), yaco0006@umn.edu (E.S. Yacoub), rega0026@umn.edu (K.R. Cullen).

http://dx.doi.org/10.1016/j.pscychresns.2015.11.002
0925-4927/

Sakai et al., 2011; Li et al., 2012; Beucke et al., 2013; Kang et al., 2013; Gruner et al., 2014; Weber et al., 2014), but only four have been in children and adolescents (Fitzgerald et al., 2010, 2011; Gruner et al., 2014; Weber et al., 2014).

R-fMRI studies in adults show interesting findings in whole brain analyses using striatal seeds. Harrison et al. (2009) found reduced functional connectivity between the dorsal striatum and the lateral prefrontal cortex and between the ventral striatum and the midbrain ventral tegmental area in 21 adults with OCD (most were medicated) compared with 21 matched healthy controls. They also found increased functional connectivity in adults with OCD between the ventral caudate/accumbens and the orbitofrontal cortex (OFC) and surrounding areas. Similar to Harrison et al. (2009), Sakai et al. (2011) found significantly greater functional connectivity between the ventral striatum and the frontal cortex in 20 medication-free adults with OCD compared with 23 matched healthy controls. Our seeds included the seeds in Harrison et al. (2009) and Sakai et al. (2011).

Beucke et al. (2013) evaluated resting-state functional connectivity in both medicated and unmedicated adults with OCD and healthy controls. Data were analyzed using a graph theory approach in contrast with previous studies that used a whole brain seed-based approach. This study found significantly greater distant connectivity in the OFC and subthalamic nucleus in the unmedicated OCD group compared with healthy controls. Buecke et al. defined distant connectivity to be connectivity to any brain regions that was more than 12 mm from the OFC (or subthalamic nucleus). The study also reported greater local connectivity in the OFC and putamen in unmedicated OCD patients compared with healthy controls.

Given that OCD may have a neurodevelopmental etiology and that the networks of interest in OCD undergo considerable refinement throughout childhood and adolescence (Huyser et al., 2009), examination of OCD circuitry in youth is critical. Fitzgerald et al. (2010) found deceased connectivity between the dorsal anterior cingulate cortex (ACC) and right anterior operculum and between the ventral medial frontal cortex and posterior cingulate cortex (PCC) in youths with OCD ($n=18$) compared with matched healthy controls ($n=18$). Twelve of the OCD participants were on selective serotonin reuptake inhibitors (SSRIs). Subsequently, Fitzgerald et al. (2011) examined resting-state functional connectivity between OCD and controls in four developmental age groups: children (8–12 years) ($n=11$), adolescents (13–17) ($n=18$), young adults (18–25) ($n=18$), and older adults (26–40) ($n=13$). Half of the OCD participants were on psychotropic medications. The seeds in Fitzgerald et al.'s (2011) study (i.e., dorsal striatum) overlapped with seed placement in the current study. Across all age groups, OCD patients compared with controls showed greater connectivity between ventral medial frontal cortex and dorsal striatum. However, only children with OCD showed significantly lower connectivity between rostral ACC and dorsal striatum, and between dorsal ACC and medial dorsal thalamus. Lower connectivity in the rostral ACC-dorsal striatum connection was associated with greater severity on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997). The findings suggest that developmental stage affects the pathophysiology of the disorder.

To date, R-fMRI studies show contrasting findings regarding whether CSTC connections in OCD patients are hypoconnected (Jang et al., 2010; Posner et al., 2013), hyperconnected (Sakai et al., 2011; Beucke et al., 2013; Kang et al., 2013), or both (Harrison et al., 2009; Fitzgerald et al., 2011). The current pilot study was designed to address some of the gaps in the literature with respect to resting-state functional connectivity in OCD. Our study investigated pediatric OCD and used advanced acquisition schemes that were developed at our University as part of the NIH-funded Human Connectome Project (HCP) to enable collection of fMRI data at much higher temporal and spatial resolution than has been standard (Feinberg et al., 2010; Moeller et al., 2010). While previous OCD studies collected data over short time periods (i.e., 4 to 8 min) (e.g., Harrison et al., 2009; Jang et al., 2010; Fitzgerald et al., 2011; Sakai et al., 2011), this study evaluated connectivity over 24 min. Lastly, we employed rigorous methods to minimize regions of interest (ROI) registration errors and to correct for confounds due to motion (Power et al., 2012).

In the current study, we viewed the striatal areas (caudate, putamen, and nucleus accumbens) as key central regions within the CSTC circuitry to interrogate this network in adolescents with and without OCD. It was hypothesized that adolescents with OCD would show abnormalities in functional connectivity in the CSTC network (i.e., between caudate/putamen/nucleus accumbens and other regions within this network, e.g., frontal cortex, thalamus) when compared with healthy controls, as measured by R-fMRI.

2. Methods

2.1. Participants

Seventeen adolescents with OCD ages 12–19 years and 13 age- and gender-matched healthy controls were enrolled. *Inclusion Criteria* for OCD participants: OCD as the primary DSM-IV diagnosis based on Anxiety Disorders Interview Schedule (ADIS) for DSM-IV, Child Version (Silverman and Albano, 1996). *Exclusion Criteria:* Lifetime diagnosis of autism/pervasive developmental disorder, bipolar disorder, schizophrenia, or substance abuse/dependence on ADIS, IQ < 80 on Wechsler Abbreviated Scales of Intelligence (WASI) (Wechsler, 1999), positive urine drug screen or pregnancy test, and MRI-incompatible features (e.g., metal implants, claustrophobia).

2.2. Procedure

The study was approved by the University Institutional Review Board. Participants were recruited from the Child and Adolescent Anxiety Disorders Clinic at our University, area clinics, newspapers, Craig's List and Facebook advertisements, and community postings. After written informed consent and assent were obtained, trained interviewers administered a 2–3 hour diagnostic assessment. Participants underwent neuroimaging at the Center for Magnetic Resonance Research and received monetary compensation for participation.

2.3. Assessment instruments

(1) *ADIS* was used to confirm OCD diagnosis (Silverman et al., 2001; Wood et al., 2002). (2) *Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and Checklist* is a clinician-rated semi-structured instrument to assess severity and types of obsessions and compulsions (Scahill et al., 1997). It has good inter-rater reliability and validity (Storch et al., 2006). (3) *Yale Global Tic Severity Scale* was used to evaluate severity of comorbid tics (Leckman et al., 1989). (4) *Child Obsessive–Compulsive Impact Scale – Revised (COIS-R), Parent Version and Child Version* measured functional impairment due to OCD (Piacentini et al., 2007). (5) *WASI* provided a measure of cognitive functioning to ensure IQs > 79.

2.4. MRI

Imaging was conducted on the Siemens Skyra 3T Human Connectome scanner (http://www.humanconnectome.org/about/project/MR-hardware.html) using a 32-channel receive only head coil. *Anatomic Acquisition:* Whole brain anatomical data with T1 contrast were acquired in 5 min using an MP-RAGE sequence with 1 mm isotropic resolution (TR = 2530 ms, TE = 3.52 ms, TI = 1100 ms, flip angle = 7°). *Processing and Analysis:* T1 images were processed using FreeSurfer version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/). Specific FreeSurfer-defined ROIs of the CSTC network (bilateral caudate, putamen, and nucleus accumbens) were identified.

2.5. R-fMRI acquisition

Resting-state BOLD data were collected using a novel multi-band EPI pulse sequence that allows for simultaneous acquisition of multiple slices (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013). Two 12-min consecutive resting scans were acquired. The two consecutive R-fMRI datasets were acquired with identical scan parameters (TR = 1.15 seconds, TE = 30 ms, voxel size = 2 mm isotropic, 60

Please cite this article as: Bernstein, G.A., et al., Abnormal striatal resting-state functional connectivity in adolescents with obsessive–compulsive disorder. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.11.002