Progress in Neuro-Psychopharmacology & Biological Psychiatry 53 (2014) 129–136

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

A preliminary study of functional connectivity of medication naïve children with obsessive–compulsive disorder

Alexander Mark Weber [a], Noam Soreni [a,b,c,*], Michael David Noseworthy [a,d,e,f]

[a] School of Biomedical Engineering, McMaster University, Hamilton, Ontario, Canada
[b] Department of Psychiatry and Behavioural Neuroscience, McMaster University, Hamilton, Ontario, Canada
[c] Offord Centre for Child Studies, McMaster Children's Hospital, Hamilton, Ontario, Canada
[d] Electrical & Computer Engineering, McMaster University, Hamilton, Ontario, Canada
[e] Medical Physics & Applied Radiation Sciences, McMaster University, Hamilton, Ontario, Canada
[f] Department of Radiology, McMaster University, Hamilton, Ontario, Canada

ARTICLE INFO

Article history:
Received 3 September 2013
Received in revised form 7 March 2014
Accepted 1 April 2014
Available online 12 April 2014

Keywords:
Cingulate network
Cortico-striatal–thalamic–cortical (CSTC)
Independent component analysis (ICA)
Obsessive–compulsive disorder
Pediatric
Resting state networks (RSN)

ABSTRACT

Background: Evidence suggests that obsessive–compulsive disorder (OCD) is associated with a dysfunction in the cortico-striatal–thalamic–cortical (CSTC) circuitry. Resting state functional connectivity magnetic resonance imaging (rs-fcMRI) allows measurements of resting state networks (RSNs), brain networks that are present at 'rest'. However, although OCD has a typical onset during childhood or adolescence, only two other studies have performed rs-fcMRI comparisons of RSNs in children and adolescents with OCD against healthy controls.
Methods: In the present study, we performed resting state functional magnetic resonance imaging using a 3 Tesla MRI, in 11 medication-naïve children and adolescents with OCD and 9 healthy controls. In contrast to previous studies that relied on a priori determination of RSNs, we determined resting state functional connectivity with a data-driven independent component analysis (ICA).
Results: Consistent with previous reports in healthy adults, we identified 13 RSNs. Case–control un-adjusted statistical significance ($p < 0.05$) was found for two networks. Firstly, increased connectivity (OCD > control) in the right section of Brodmann area 43 of the auditory network; Secondly, decreased connectivity in the right section of Brodmann area 8 and Brodmann area 40 in the cingulate network.
Conclusions: Our preliminary findings of case–control differences in RSNs lend further support to the CSTC hypothesis of OCD, as well as implicating other regions of the brain outside of the CSTC.

1. Introduction

Obsessive–compulsive disorder (OCD) is a common neuropsychiatric disorder with a lifetime prevalence of between 1 and 2.5% (Bebbington, 1998; Horwath and Weissman, 2000; Ruscio et al., 2010). Lifetime prevalence of OCD for children and adolescents has been estimated to be around 0.25–2.7% (Heyman et al., 2003; Rapoport et al., 2000), which increases exponentially with increasing age (up to 18) (Heyman et al., 2003). OCD in children and adolescents is associated with functional impairments in home, school and social settings (Valderhaug and Ivarsson, 2005).

Structural and functional neuroimaging studies of youth and adults with OCD suggest an impairment of cortico-striatal–thalamic–cortical (CSTC) circuits (Graybiel and Rauch, 2000; Saxena et al., 1998, 2001). Recently, a growing number of functional magnetic resonance imaging (fMRI) studies have been used to probe CSTC activation in OCD using an experimental 'resting' state, in which the subject is asked to simply relax, remain awake and not to think of anything in particular (Biswal et al., 1995).

Resting state fMRI is often analyzed using a functional connectivity approach termed resting state functional connectivity MRI (rs-fcMRI) (Damoiseaux et al., 2006). rs-fcMRI analysis usually targets low frequency (<0.1 Hz), synchronized activations (also known as low-frequency blood oxygen level dependent (BOLD) fluctuations) in spatially separated areas of the brain (Friston et al., 1993). These synchronized neuro-physiological events, active at rest, represent structurally and functionally connected

Abbreviations: OCD, obsessive–compulsive disorder; CSTC, cortico-striatal–thalamic–cortical; MRI, Magnetic Resonance Imaging; rs-fcMRI, resting state functional connectivity magnetic resonance imaging; RSN, resting state network; ICA, independent component analysis; BOLD, blood oxygen level dependent; CCA, cross-correlation-analysis; ROI, region of interest; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; K-SADS-PL, Kiddie-Sads-Present and Lifetime; REB, Research Ethics Board; CY-BOCS, Child Yale–Brown Obsessive–Compulsive Scale; MELODIC, Multivariate Exploratory Linear Optimized Decomposition into Independent Components; FWHM, full-width-at-half-maximum; BA, Brodmann area; DMN, default mode network; mPFC, medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex.

* Corresponding author at: Pediatric OCD Consultation Team, Anxiety Treatment and Research Center, St. Joseph's Healthcare, 50 Charlton Ave. East, Hamilton, Ontario L8N 4A6, Canada. Tel.: +1 905 522 1155x33139.
E-mail address: nsoreni@sjtoes.ca (N. Soreni).

http://dx.doi.org/10.1016/j.pnpbp.2014.04.001
0278-5846/

networks, termed resting state networks (RSNs). rs-fcMRI can be analyzed by two different approaches: one that uses strong a priori knowledge, and the other which is almost exclusively data driven (Ma et al., 2007). Most rs-fcMRI analyses to date have used cross-correlation-analysis (CCA), an a priori driven method, which looks at correlations between each voxel and a pre-determined function (Biswal et al., 1995; Ma et al., 2007). This pre-determined function is often taken to be a preselected region of interest (ROI), or seed-voxel. In contrast, independent component analysis (ICA; McKeown et al., 1998), lacks an ROI a priori assumption. Instead, ICA is based on the assumption that activations are independent to other signal variations (motion, cardiac and respiratory fluctuations, etc.), and extract components (RSNs) based on enforcing orthogonality spatially.

To date, there have been 11 published rs-fcMRI studies in OCD that we have found (Fitzgerald et al., 2010, 2011; Fontenelle et al., 2012; Harrison et al., 2009; Jang et al., 2010; Kang et al., 2013; Li et al., 2012; Meunier et al., 2012; Sakai et al., 2010; Stern et al., 2012a; Zhang, 2011), all of which had relied on a CCA approach with seed-voxels placed in various regions of the brain and reported statistically significant differences between patients and controls.

Although OCD has a high rate of onset during childhood and adolescence, only two rs-fcMRI studies (Fitzgerald et al., 2010, 2011) have focused on children and adolescents with the disorder. This is of particular importance given that RSNs in healthy subjects go through many developmental changes during the transition from childhood to adulthood (Fair et al., 2008, 2009; Stevens et al., 2009; Supekar et al., 2010). The first rs-fcMRI study that looked at children and adolescents (Fitzgerald et al., 2010) reported decreased connectivity between the dorsal anterior cingulate cortex (ACC) and right anterior operculum, as well as between the ventral medial frontal cortex and the posterior cingulate cortex (PCC), in OCD patients as compared to healthy controls. The second study (Fitzgerald et al., 2011) reported decreased connectivity between the dorsal striatum and rostral ACC, two structures that were not the focus of their initial report (Fitzgerald et al., 2010). Thus, preliminary RSN findings in youth with OCD support the hypothesis that differences in RSN activation exist between children and adolescents with OCD and their healthy counterparts. However, evidence is currently limited by the small number of studies and the reliance on a CCA analysis approach in existing studies.

The present fMRI pilot study compared resting state activations between medication naïve children and adolescents with OCD and healthy controls. Unlike previous reports, we opted to use ICA as it provides a data-driven analysis of the resting state fMRI data and minimizes dependency on seed-voxel location and inter-subject anatomical variability. As this was the first study to use ICA in children and adolescents with OCD, we did not limit ourselves to pre-determined RSNs, but instead decided to compare all identifiable RSNs between patients with OCD and healthy controls. We hypothesized, based on the study by Fitzgerald et al. (2011) that we would find *decreased* connectivity between the cingulate cortex and caudate during 'rest' activation.

2. Methods and materials

2.1. Subjects

15 psychotropic naïve children and adolescents with OCD (age 8–16 years old) were recruited from the Pediatric OCD Consultation Team at the Anxiety Treatment and Research Center, Hamilton, Ontario. Patients had a primary diagnosis of OCD according to *DSM-IV* criteria (American Psychiatric Association, 1994). All DSM-IV diagnoses (OCD and co-morbid conditions) were made by a child psychiatrist (N.S.) using the K-SADS-PL (Kaufman et al., 1997) A total of 13 healthy comparison subjects (age 8–16 years old) were recruited from the general community through advertisements. Control subjects did not have any personal history of psychiatric illness, treatment with psychotropic medications or a diagnosed learning disability.

Exclusion criteria for patients and controls included lifetime history of psychosis, bipolar disorder, conduct disorder, substance abuse/dependence, an eating disorder, significant medical or neurologic disorders or a previously diagnosed learning disability. The St. Joseph's Healthcare Research Ethics Board (REB) approved the study. Before initiating all studies, legal guardians provided written informed consent, and all children 16 years of age and younger gave written assent. Adolescents 16 years of age and older and their parents gave written informed consent before initiating all studies.

2.2. Clinical measures

All patients were assessed for OCD symptom severity using the Child Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) (Goodman et al., 1991). The CY-BOCS is a clinician-rated semi-structured instrument with good inter-rater reliability and validity for children and adolescents (Storch, 2006). To ensure that patients had at least mild OCD symptoms, only patients with CY-BOCS total scores >11 were recruited to the imaging study (Scahill et al., 1997).

2.3. Imaging

All scanning was done on a GE Signa 3 T HDx twinspeed short bore MRI system using an 8-channel phased array receive-only head RF coil (GE Healthcare, Milwaukee, WI). Each session involved a localizer scan (30 s) and a high-resolution 3D IR-prepped fSPGR T_1-weighted imaging sequence (24 cm field of view, TE/TR/TI = 2.1/7.5/450 ms, flip angle = 12°, 512 × 512 matrix, 1 mm thick/0 mm skip, 148 acquired slices, voxels were reconstructed to 0.469 × 0.469 × 1 mm). Resting state BOLD data was acquired with a T_2*-weighted gradient echo planar imaging (GE-EPI) sequence, with the following parameters: 64 × 64 matrix, 28 axial slices (5 mm thick, no skip), TR = 2000 ms, TE = 35 ms, flip angle = 90°, 240 images per slice, and angled to AC/PC alignment. Subjects were asked to close their eyes, lay still and think of nothing in particular.

2.4. Pre-processing

Data from each subject was corrected for interleaved slice acquisition and 3D rigid body motion, and was aligned to anatomical data using the software application AFNI (Cox, 1996). Of an original participant group of 13 controls and 15 OCD subjects, 4 controls and 4 OCD subjects were excluded from analysis due to motions greater than 2 mm or degrees in single scan session. Next, using the FSL software package MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) (Beckmann and Smith, 2004), all functional data were first registered to brain-extracted high resolution T1-weighted anatomical scans, then registered to MNI152 standard space at 2 mm resampling resolution. Images were then filtered with a high-pass temporal cutoff of 0.009 Hz, and were spatially smoothed with a Gaussian kernel with full-width-at-half-maximum (FWHM) of 5 mm.

2.5. rs-fcMRI data analysis

Using MELODIC, probabilistic independent component analysis was performed on all subjects, at a single-group level, to decompose the 4D data sets into separate spatial maps. This was accomplished by using a multi-session temporal concatenation approach, which works by stacking all 2D (space(voxels) * time) data matrices of every data-set on top of each other. The concatenation method was chosen due to the fact that RSNs between subjects are not expected to have the same time-courses. The present study implemented the following options in MELODIC: time-courses were variance-normalized in order to stress voxel-wise temporal dynamics over mean signal; multi-session temporal concatenation (as already mentioned); the number of components (RSNs) was