

ORIGINAL ARTICLE

DEFAULT MODE NETWORK CONNECTIVITY DIFFERENCES IN OBSESSIVE-COMPULSIVE DISORDER

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Abstract

Recent evidence suggests that the brain intrinsic activity during rest might be as significant as task evoked activities and consumes considerable energy linked to neural signaling processes. We performed an fMRI study recently aiming to compare the differences in brain activity between patients with obsessive-compulsive disorder and healthy volunteers during a simple suppression paradigm. We hypothesized that the patients with obsessive-compulsive disorder would show default mode network (DMN) connectivity dissociations from healthy individuals. OCD patients had higher connectivity ($p < 0.05$) than controls between right inferior parietal lobe (IPL) and left ventral medial prefrontal cortex (MPFC).

Key words: *obsessive-compulsive disorder, fMRI, functional connectivity, resting activity*

1. INTRODUCTION

Human brain thought to be in an idle state during rest until recently. However, recent evidence suggests that, when a subject rests quietly without doing any particular task brain consumes considerable energy, mostly devoted to neural signaling processes (Astrup et al., 1981; Raichle et al., 2006). Thus, it is posited that the intrinsic activity during rest might be as significant as task evoked activities (Raichle et al., 2006).

A set of brain regions is “active” at eyes closed rest or during other low level control tasks and this activity decreases during goal directed tasks (Shulman & Fiez, 1997; Mazoyer et al., 2001). These areas commonly known as “default mode network” (DMN) include some posterior and ventral medial brain areas; comprising cingulate cortex, precuneus, retrosplenial cortex, ventral / dorsal medial prefrontal cortex as well as some posterior lateral areas revolving around inferior parietal cortex and superior temporal sulcus (Gusnard et al., 2001). The activity decrease in these areas suggested to represent the reallocation of resources to task demands, which would serve “default functions” during rest (Gusnard et al., 2001; Raichle et al., 2001).

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We performed an fMRI study recently aiming to compare the differences in brain activity between patients with obsessive-compulsive disorder and healthy volunteers during a simple suppression paradigm (Kocak et al., 2011). We found that patients showed less activity in right inferior parietal lobe, superior frontal gyrus (SFG) and posterior cingulate cortex (PCC), during cognitive control of a simple mental image. Interestingly, these three brain regions are part of the suggested DMN (Fox et al., 2005). We also showed that patients with worse clinical scores showed reduced SFG and PCC activity during mental suppression task. But follow up ROI analysis showed that the resting activity in SFG and PCC were higher in the patient group compared to the healthy controls suggesting a problem in DMN functionality.

The results in our recent study (explained above) inspired us to reanalyze the same data in terms of DMN functionality. We did this by use of resting state functional connectivity analysis (rs-fcMRI). This technic uses very low-frequency fluctuations (<0.1 Hz) in fMRI BOLD signal that reveal temporal correlations between brain regions that appear to define functional networks of the human brain (Biswal et al., 1995). We hypothesized that the patients with obsessive-compulsive disorder would show DMN connectivity dissociations from healthy individuals.

2. MATERIAL AND METHODS

2.1. Participants

The study included 12 right-handed (six male and six female) OCD patients (OCD group) and 12 right-handed healthy volunteers matched for gender and level of education (control group). None of the participants in the control group had a neurological disorder or DSM-IV Axis I psychiatric disorder. Among the OCD patients, eight were cleaners, three were checkers (one of the checkers also had contamination obsessions), and one had harming obsessions. None of the OCD patients had another DSM-IV Axis I psychiatric disorder.

Disease duration in the OCD group ranged from 6 months to 7years. All the participants were, at minimum, high school graduates. Written informed consent was obtained from all the participants, and sociodemographic data, medical history, and current health status were determined using a detailed questionnaire. Detailed information about the clinical scales and inventories administered to the patients could be found elsewhere (Kocak et al., 2011).

2.2. Experimental procedure

Although participants performed some mental tasks during the original experiment (Kocak et al., 2011), we used the free-imagination condition for the rs-fcMRI analysis in the presented study. In this condition, subjects were instructed to rest eyes closed in the scanner and think what ever comes to their mind (a sort of mind wandering or free-association).

A blocked fMRI design was used in the experiment. Each block lasted 25 s (five TRs). There were four functional runs: each run consisted of 15 blocks (75 TRs). In all, we obtained 300 functional images. There were 12 blocks of free-imagination containing 60 functional images.

2.3. Neuroimaging

A 1.5 Tesla Siemens Magnetom Symphony Maestro Class MRI system (Siemens, Erlangen Germany) was used for fMRI acquisition. The participants' heads were immobilized with calipers built into the head coil. A vitamin E capsule was taped to the right temporal region to mark laterality. High-resolution T1-weighted anatomical scans were obtained in the axial plane using a gradient echo sequence (time to repeat/time to echo [TR/TE]: 500/13 ms; flip angle: 45°; field of view (FOV): 256; matrix: 256 X 256; slice thickness: 1 mm). Functional

scans were acquired in the axial plane using thirty-six 5-mm slices with a 0-mm gap and an echo-planar sequence (TR/TE: 4940/36 ms; flip angle: 90°; FOV: 224; matrix: 64 X 64). The orientation of each functional scan was aligned with the anterior commissure-posterior commissure line. We obtained 79 TRs for each run. For all functional runs the first four images were excluded from analysis in order to allow for signal equilibration. There were four functional runs; as such, the data analyzed consisted of 300 images.

2.4. Image processing and data analysis

Preprocessing of the data was performed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) running in a MATLAB 7 environment (Mathworks, Sherborn, Mass., USA). The functional images were realigned to correct for movement artifacts and slice-timing correction was performed afterwards. High-resolution anatomical T1 images were coregistered with the realigned functional images to enable anatomical localization of the activations. The structural and functional images were spatially normalized into a standardized anatomical framework, based on the Montreal Neurological Institute (MNI) averaged brain and approximating the normalized probabilistic spatial reference frame of Talairach and Tournoux (Talairach & Tournoux, 1988). Model estimation included a high-pass filter (128 s). Smoothing was performed with a 9-mm full-width half-maximum Gaussian kernel.

Rs-fcMRI analysis was performed on the preprocessed data with conn software (<http://www.nitrc.org/projects/conn/>). Physiological and other spurious sources of noise were estimated and removed together with movement-related covariates (Whitfield-Gabrieli et al., 2011). The residual BOLD time-series were band-pass filtered to leave low-frequency BOLD oscillations ($0.004 \text{ Hz} < f < 0.08 \text{ Hz}$). To perform seed driven connectivity analysis ROIs were defined on PCC and medial prefrontal cortex (MPFC) regions that are the representative DMN areas (Fox et al., 2005 ; Whitfield-Gabrieli et al., 2011) Left and right inferior parietal lobe (IPL) regions were also included as ROIs to ask if there are any connectivity differences in these regions between OCD patients and healthy controls as a follow up analysis for our recent findings (Kocak et al., 2011). Extracting the residual BOLD time course from seed regions, and computing Pearson's correlation coefficients between that time course and the time course of all other voxels produced correlation maps. Correlation coefficients were converted to normally distributed scores using Fisher's transform to allow for second-level General Linear Model analyses. Second-level analyses compared the whole-brain connectivity patterns of patients and controls related to the four seeds. All analyses have voxel level uncorrected threshold of $p < 0.001$ and FWE ($p < 0.05$) correction at the cluster level.

Table 1. The functional connectivity differences between the patients with obsessive-compulsive disorder (OCD) and healthy controls (CONT) for four seeds.

Seed	connected anatomic region	x y z	BA	# voxels	T-score
CONT > OCD					
PCC	Left middle/superior temporal gyrus	-60 -2 -8	21/22	99	6.16
OCD > CONT					
Left IPL	Left extrastriate cortex	-22 -90 14	18/19	154	6.47
Right IPL	Left ventral MPFC	-2 54 6	32/10	114	5.69
MPFC	Left cerebellum posterior lobe	-2 -64 -50		114	5.34

Note: OCD > CONT means the connectivity is more in OCD patients than controls and CONT > OCD means vice versa. IPL: Inferior parietal lobe. MPFC: Medial prefrontal cortex. PCC: Posterior cingulate cortex. BA:

Brodmann area. All the coordinates are given in Montreal Neurological Institute (MNI) space. $P < 0.05$ FWE cluster corrected.

3. RESULTS

Rs-fc-MRI analysis was performed on PCC (0, -56, 28), MPFC (0, 54, -8), left IPL (-42, -68, 38) and right IPL (48, -60, 38) ROIs (center coordinates in MNI space are given in parenthesis). Healthy controls had higher connectivity ($p < 0.05$) than OCD patients between PCC and left middle/superior temporal gyrus (BA 21, BA 22) (Figure 1, please see Table 1 for the results). OCD patients had higher connectivity ($p < 0.01$) than controls between left IPL and left extrastriate cortex than controls (BA 18, BA 19) (Figure 2b). OCD patients had higher connectivity ($p < 0.05$) than controls between right IPL and left ventral MPFC (BA 32, BA 10) (Figure 2a). Finally, OCD patients also had higher connectivity ($p < 0.05$) than controls between MPFC and posterior lobe of left cerebellum (Figure 2c).

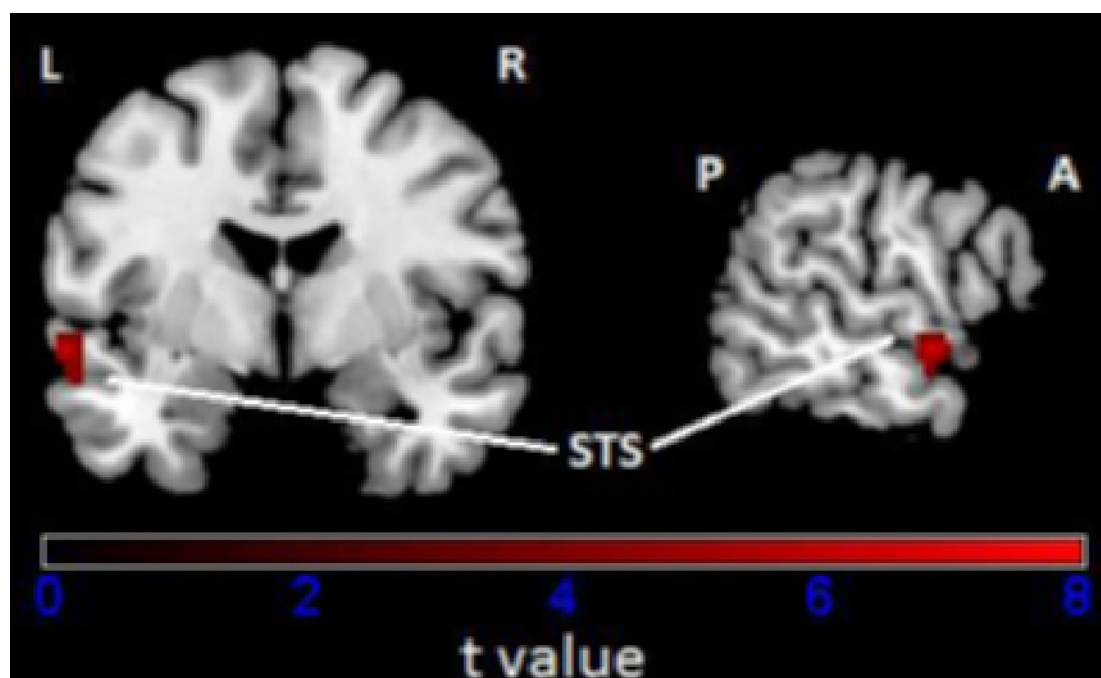


Figure 1. Resting functional connectivity difference between healthy controls and obsessive-compulsive disorder (OCD) patients for posterior cingulate cortex (PCC) seed. The healthy controls showed higher connectivity between PCC and left middle/superior temporal gyrus than OCD patients. $P < 0.05$ FWE cluster corrected. STS: Superior temporal sulcus. L: Left. R: Right. P: Posterior. A: Anterior.

4. DISCUSSION AND CONCLUSIONS

We asked if there is a DMN connectivity problem in OCD patients. To answer this question, we performed rs-fc-MRI analysis comparing the OCD patients and healthy controls, using previously published DMN areas as seed regions; namely PCC, MPFC and bilateral IPL (Fox et al., 2005; Whitfield-Gabrieli et al., 2011). While discussing the results, we conceptualized the resting as a physiologic, functionally significant state of the brain and that correlated spontaneous low-frequency fMRI BOLD signal oscillations could facilitate the coordination and organization of information processing (Buzsaki & Draguhn, 2004; Raichle et al., 2006).

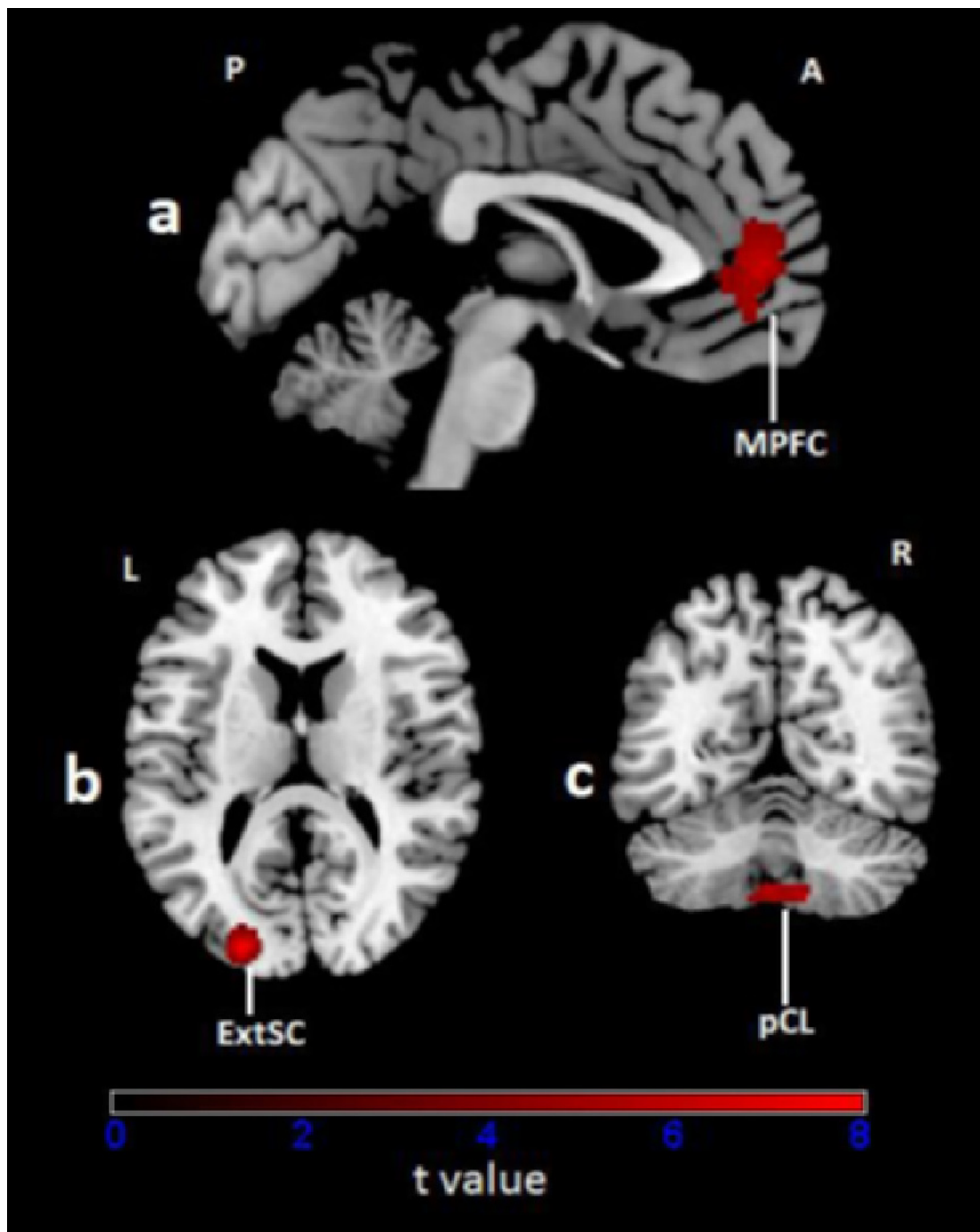


Figure 2. The functional connectivity differences between the groups for inferior parietal lobe (IPL) and medial prefrontal cortex (MPFC) seeds (a) Obsessive-compulsive disorder (OCD) patients had higher connectivity between right IPL and left ventral MPFC than healthy controls. (b) OCD patients had higher connectivity between left IPL and left extrastriate cortex (ExtSC) than controls. (c) OCD patients also had higher connectivity between MPFC and left posterior cerebellar lobe (pCL) than controls. $P < 0.05$ FWE cluster corrected. L: Left. R: Right. P: Posterior. A: Anterior.

Healthy controls showed higher connectivity between PCC and left superior temporal sulcus region (Fig1). Activity in PCC in baseline condition is suggested to be related to the processing the information coming from the environment around us or inside us (Gusnard et al., 2001). It is also suggested that PCC involves in episodic memory and imagery processes

(Cabeza et al., 2002). Although inferior temporal cortex is mostly implicated in the default mode network, superior temporal sulcus (STS) region is also reported to show resting state activity (Shulman & Fiez, 1997; Raichle et al., 2006). STS region is suggested to take role in processing of biological motion (Allison et al., 2000). Specifically, observing or imagining movements of the body parts (for example hand) activated cortex revolving around STS (Stephan et al., 1995; Allison et al., 2000).

It was reported that the connectivity pattern of PCC during a visual processing task was nearly identical to the one obtained during resting state fMRI data, suggesting that the default mode neural network is minimally disrupted by sensory processing tasks with limited cognitive demand (Greicius et al., 2003). We suggest that lower resting state connectivity between PCC and STS region might underlay some of the problems OCD patients demonstrate. Decreased connectivity between these regions may cause decreased imprinting of persons own body part movements to their episodic memory. This mechanism might explain some of the repetitive movements of OCD patients.

OCD patients (compared to the controls) showed higher connectivity between right IPL and MPFC also between left IPL and left extrastriate cortex. MPFC and extrastriate cortex are involved in the DMN. It has been proposed that in humans sensory representation of a situation that requires a decision may activate MPFC which might hold nondeclarative dispositional knowledge related to the individual's previous emotional experience about similar situations (Bechara et al., 1997). Right IPL is reported to involve in the mental manipulation of 3D images (Suchan et al., 2006) and orienting attention globally (Cicek et al., 2007). Thus we suggest that higher connectivity of right IPL with MPFC may cause higher noise related to the previous personal experiences during spatial tasks, which may or may not require decision. This heightened noise could cause the malfunction of one of or both regions. This suggestion also explains our previous finding that OCD patients showed lower IPL activity during simple imagination tasks compared to the controls (Kocak et al., 2011).

Left IPL was suggested to take role in mental representation of action (Peran et al., 2010). Specifically, it was suggested to engage during retrieval of spatial-temporal features of object manipulation (grasping and manipulation of any object). Patients showed higher connectivity between left IPL and left extrastriate cortex. This resting connectivity pattern might affect tasks like object grasping in a way, which must be explained by additional findings.

Finally patients showed again higher connectivity between MPFC and cerebellum. Although coordinates are somehow apart from our findings cerebellum was also implicated in the DMN (Mazoyer et al., 2001; Fox et al., 2005). If we again assume higher connectivity creates higher noise causing MPFC dysfunction, then previous experiences may affect instantaneous decisions about movements. This assumption may have some significance for some of the symptoms of OCD patients.

In summary, our findings suggest rs-fc-MRI differences between OCD patients and healthy controls. If we assume resting as a physiologic, functionally significant state of the brain these differences might underlay mechanisms of some of the problems manifested in OCD patients.

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