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Short communication

The resting-brain of obsessive–compulsive disorder

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ABSTRACT

Obsessive–compulsive disorder (OCD) is one of the most debilitating psychiatric conditions, having a dramatic impact on patients' daily living. In this work, we aimed to explore resting-state functional connectivity in OCD patients, using an independent component analysis. Eighty individuals (40 patients and 40 healthy controls) performed a resting state fMRI protocol. OCD patients displayed reduced functional connectivity (FC) in visual and sensorimotor networks. In addition, patients displayed decreased FC between sensory networks and increased FC between default-mode and cerebellar networks.

1. Introduction

Obsessive–compulsive disorder (OCD) is a psychiatric condition characterized by the presence of obsessive thoughts and compulsions. It has an estimated prevalence of 1–3% (Karno et al., 1988; Ruscio et al., 2010) and constitutes one of the most debilitating psychiatric disorders with a severe impact on patients' daily life. While OCD patients are typically aware of the nonsensical nature of their obsessions and compulsions, they are not able to control these symptoms (Graybiel and Rauch, 2000).

Meta-analytic aggregations of neuroimaging studies suggest that OCD is characterized by marked neurobiological alterations in structural and functional modalities. Structurally, OCD is characterized by consistent volumetric grey matter volume (GMV) alterations, including increases in the left postcentral gyrus, middle frontal, putamen, thalamus and culmen while displaying decreased GMV in occipital regions in temporal and insular regions (Eng et al., 2015). Patients with OCD display impairments in executive function domains [including response inhibition (Menzies et al., 2007), interference (Schlösser et al., 2010) and set-shifting (Shin et al., 2014)], visuospatial and verbal memory (Shin et al., 2014), over-reliance on habits (Gillan et al., 2011) or emotional processing (Thorsen et al., 2018). Neurobiologically, these deficits are thought to be associated with abnormal functioning within cortico-striato-thalamo-cortical (CTSC) loops (Milad and Rauch, 2012; Thorsen et al., 2018), but also including the cerebellum and the parietal cortex (Eng et al., 2015).

A recent review of studies examining seed-based functional connectivity (FC) during rest demonstrated consistent reduced connectivity within and between frontoparietal (FPN), salience (SN), and default-mode (DMN) networks (Guersel et al., 2018). Increased amplitude of low-frequency fluctuation (ALFF) in the OFC, anterior cingulate cortex (ACC) and reduced ALFF in cerebellum and parietal cortex (Hou et al., 2012), as well as increased striatal-OFC FC (Jung et al., 2013) has also been reported.

Model-free characterization of the resting-state FC among different resting-state networks is considerably less explored. Among this pool of studies, it has been reported that OCD is characterized by increased FC **between** the caudate, putamen and the cerebellum (Vaghi et al., 2017); on the other hand, reduced FC in the cerebellum, as well as in occipital and temporal cortices has been reported (Hou et al., 2014; Moreira et al., 2017). To the best of our knowledge, only four studies have examined resting-state FC using Independent Component Analysis (ICA) in OCD (Cheng et al., 2013; Fan et al., 2017; Gruner et al., 2014; Weber et al., 2014). From these, only one analyzed between-networks' FC. With this work, we aimed to complement the existing literature by exploring the patterns of within and between resting-state networks' FC, using an ICA approach.

2. Methods

2.1. Subjects

Forty OCD patients and 40 healthy controls (matched for sex, age and education) participated in this study. All participants were right-

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handed and had no history of neurological or comorbid disorders. OCD patients (all receiving medication) were characterized with a comprehensive clinical assessment (see Table S1). A semi-structured interview based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-TR and the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS, (Goodman et al., 1989)) were administered to establish the OCD diagnosis. Anxiety and depression levels were assessed using the Hamilton Anxiety (HAM-A) and Hamilton Depression (HAM-D) scales, respectively. The study was conducted according to the Declaration of Helsinki principles and was approved by the Ethics Committee of Hospital de Braga (Portugal). The study goals were explained, and written informed consent was obtained from each participant. Imaging was performed using a clinical approved 1.5 T Siemens Magnetom Avanto MRI Scanner (Siemens, Erlangen, Germany). The acquisition and preprocessing parameters of structural and functional MRI sequences are detailed in File S1.

2.2. Independent component analysis and identification of resting-state networks

Resting-state network (RSN) maps were analyzed voxel-wise through a probabilistic independent component analysis (PICA) as implemented in Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC), distributed with FSL (Beckmann and Smith, 2004). PICA is a fully data-driven approach that enables the isolation of components based on the temporal correlation of the corresponding areas, while maximizing the spatial independence between components. Dual-regression analysis was performed to estimate the subject-specific components that correspond to the group-wise RSNs. Because the PICA approach may identify noisy components corresponding to non-biological signal, such as movement artifacts, the independent components were selected after visual inspection of their spatial distribution (Horowitz-Kraus et al., 2015). Specifically, components that were mainly present in regions that do not generate the blood-oxygen-level-dependent (BOLD) signal (white matter, ventricles or outside the brain) were excluded from the analysis.

2.3. Statistical analysis

Statistical group comparisons were conducted using two-samples tests, adjusted for confounding factors (sex and age). Intra-RSN FC was compared between groups, using a non-parametric permutation procedure implemented in the randomize tool from FSL (Winkler et al., 2014). Threshold-free cluster enhancement (TFCE) was used to detect widespread significant differences and control the family-wise error rate (FWE-R) at $\alpha = 0.05$. 5000 permutations were performed for each contrast. For the analysis of inter-RSN FC, the time-series of each RSN were extracted and using the Fisher's Z-transformed Pearson correlation coefficients, matrices of functional connectivity between pairs of RSNs were created. Individual correlations were statistically compared ($\alpha = 0.05$ with FDR correction) between groups.

3. Results

Twenty-two components were obtained from the PICA. Fifteen of these components were found to be representative of the most typical RSNs (Fig. 1a). OCD patients displayed reduced FC within the primary visual (PVN), high visual (HVN) and sensorimotor (SMN) networks (Supplementary Information). Specifically, for the PVN, there were significant differences between groups in one large cluster (2465 voxels), with peaks on the left calcarine and the left lingual gyrus; for the HVN, patients had decreased FC in six clusters with peaks in distinct occipital subdivisions; for the SMN, OCD patients had significantly decreased FC in one cluster comprising the paracentral and the supplementary motor area of the left hemisphere (Fig. 1, Table S2).

Regarding the inter-RSN FC, despite the fact that several patterns of altered FC between distinct RSNs were observed in OCD patients, the only findings remaining statistically significant after correction for multiple comparisons (bold lines) were reduced PVN-SMN ($t_{(79)} = 5.73$, $p < .001$) and increased DMN-cerebellar FC in OCD patients. The patterns of altered FC between different RSNs in OCD patients are graphically displayed on Fig. 1. No significant results were obtained regarding the association between within/between FC and clinical variables.

4. Discussion

In this work, we observed that OCD patients are characterized by reduced FC within and between visual and sensorimotor networks, as well as increased cerebellar-DMN FC.

Reduced FC within the visual network in OCD patients complements our previous findings (Moreira et al., 2017) and highlights the relevance of sensorial-related deficits in several psychiatric conditions, including maniac and depressed groups of patients with bipolar disorder (Shaffer et al., 2018). These results are in accordance with the hypothesis that one of the mechanisms underlying the OCD phenotype relies on the deactivation of occipital/parietal regions which are associated with the visual-perceptual processing of incoming rich stimuli (Gonçalves et al., 2010). Previous research has highlighted that the visual network is involved on the allocation of attentional (particularly, visual) resources, such that an increased FC within this network is thought to reflect a greater demand on the allocation of resources (Horowitz-Kraus et al., 2015). In addition, the activity of these regions was previously associated with the generation of somatic arousal, possibly indicating that modulation through arousal is adaptive in order to promote an easier processing of relevant visual information (Gauthier et al., 1997). Altogether, this pattern of reduced FC within and between these networks may play a relevant role for the pathophysiology of the disorder, particularly with the generation of obsessive thoughts.

In addition, there was a significantly increased FC between the DMN and the cerebellar network in the group of OCD patients. Previous reports have described abnormal DMN-cerebellum FC in distinct psychiatric conditions, including major depression disorder, schizophrenia or bipolar disorder, however such alterations were not previously established in the case of OCD. Notwithstanding, such results reinforce the role of the cerebellum for the pathophysiology of OCD – a region with reciprocal connections with CSTC regions (Eng et al., 2015). Our findings are inconsistent with a previously reported reduced cerebellar-DMN FC in OCD patients (Xu et al., 2018). However, it is important to highlight some important differences between these studies: first, the abovementioned study relied on a seed-based analysis for the examination of cerebellum-cerebral FC patterns; second, our results were obtained only with the dorsal division of the DMN. Considering this, while it is reasonable to hypothesize that our findings may reflect a compensatory reallocation or dedifferentiation between these networks (Guo et al., 2015), additional studies are required to clarify this hypothesis.

Our sample of OCD patients was under pharmacological treatment. As such, it is relevant to highlight that our positive and null findings may be importantly influenced by the medication itself. Thus, future studies assessing drug-naïve OCD patients are needed to tackle this confounding effect.

In sum, our study offers evidence for the involvement of altered sensorial-related patterns of brain FC, which may underline distinct mood states, as suggested in other psychiatric conditions (Shaffer et al., 2018).

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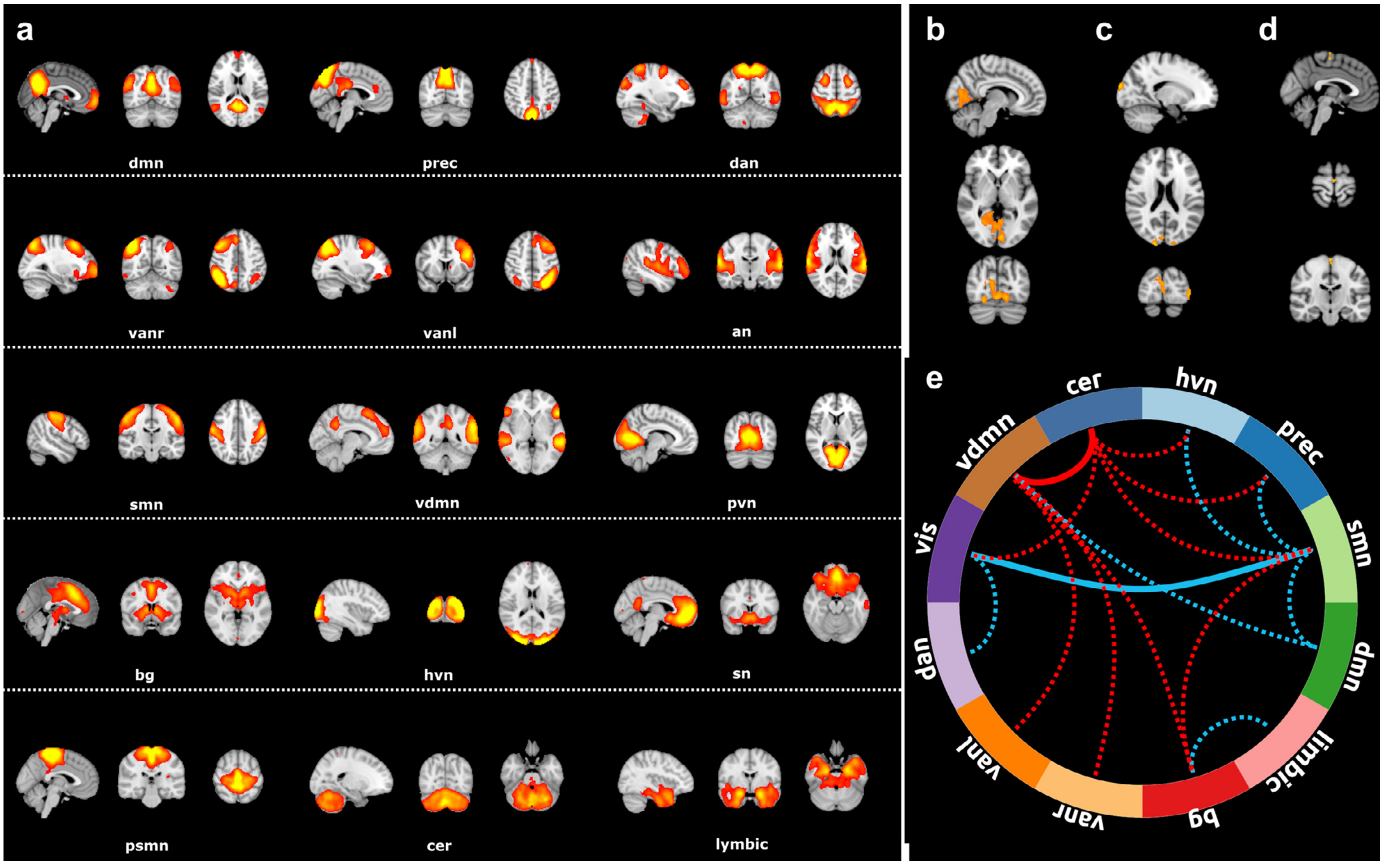

Fig. 1. Resting state networks. (a) Resting state networks identified through ICA. Group ICA maps thresholded at $Z > 3.09$ (dmn, default mode network; prec, precuneus network; dan, dorsal attention network; vanr, ventral attention network – right; vanl, ventral attention network – left; an, auditory network; smn, sensorimotor network; vdmn, ventral DMN; pvn, primary visual network; bg, basal ganglia network; sn, salience network; psmn, primary sensorimotor network; cer, cerebellar network; limbic, limbic network); (b) group differences within the primary visual network; (c) group differences within the high visual network; (d) group differences within the sensorimotor network; (e) group differences between resting-state networks. Dashed and bold lines represent uncorrected and corrected for multiple-comparisons differences (red lines: associations significantly increased in the OCD group; blue lines: associations significantly reduced in the OCD group). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.06.008.

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