Inferior frontal gyrus white matter abnormalities in obsessive–compulsive disorder

Óscar F. Gonçalvesa,b,c, Sónia Sousa c, Liliana Maia c, Sandra Carvalhoad,c, Jorge Leitéa,c, Ana Ganhoc, Ana Fernandes-Gonçalved, Brandon Frankb, Fernando Pocinhoe, Angel Carracedof and Adriana Sampaio c

The aim of the present study is to explore obsessive–compulsive disorder (OCD)-related abnormalities in white matter connectivity in OCD for a core region associated with inhibitory control [i.e. inferior frontal gyrus (IFG)]. Fifteen patients with OCD (11 men) and 15 healthy controls (nine men) underwent diffusion tensor imaging scanning to study four diffusivity indexes of white matter integrity [fractional anisotropy, mean diffusivity (MD), axial diffusivity and radial diffusivity (RD)]. The results showed that persons with OCD manifested significantly lower fractional anisotropy levels in the bilateral IFG as well as its parcellations in the pars opercularis, pars triangularis, and pars orbitalis. Significantly higher levels of MD, RD were evident for the OCD group in the IFG as a whole as well as in the bilateral subregions of the pars triangularis and pars opercularis (for MD and RD), the right side of the pars orbitalis (for RD), and the left side of the pars triangularis and right side pars opercularis (for axial diffusivity). Overall, the results suggest significant alterations in structural connectivity, probably associated with myelination and axonal abnormalities in the IFG of OCD patients. NeuroReport 26:495–500 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

NeuroReport 2015, 26:495–500

Keywords: connectivity, inferior frontal gyrus, obsessive–compulsive disorder, pars opercularis, pars orbitalis, pars triangularis

aDepartment of Physical Medicine and Rehabilitation, Spaulding Center of Neuromodulation, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, bBouvé College of Health Sciences, Northeastern University, Boston, Massachusetts, USA, cNeuropsychophysiology Lab, CIPs; School of Psychology, University of Minho, Braga, dCUF Porto Hospital, Department of Psychiatry, Porto, eDepartment of Psychiatry, University of Coimbra Hospitals, Coimbra, Portugal and fForensic Genetics Unit, University of Santiago de Compostela, Santiago de Compostela, Spain

Correspondence to Óscar F. Gonçalves, PhD, Spaulding Neuromodulation Center, Spaulding Rehabilitation Hospital, Charlestown campus: 79/96, 13th Street, Charlestown, MA 02129, USA
Tel: +1 617 952 6153; fax: +1 617 952 6060; e-mail: ocoelhonevesgoncalves@partners.org

Received 8 April 2015 accepted 13 April 2015

Introduction

Obsessive–compulsive disorder (OCD) is a disabling psychiatric condition, with a lifetime prevalence of around 2–3%, characterized by difficulties inhibiting intrusive negative thoughts, images, and ritualized behaviors [1]. Obsessions and compulsions have been associated with failures in inhibitory processes in various experimental tasks (e.g. Stroop task; Flanker task, Simon Task) [2,3].

At the neural level, the inhibition of prepotent cognitions or behaviors seems to be dependent on the structural and functional integrity of the cortico-striatal-thalamic-cortical loop (CSTC) [4]. There is now consistent evidence of alterations in CSTC pathways in individuals with OCD. For example, structural alterations in gray matter have been reported in brain regions of the CSTC [5]. Similarly, the provocation of OCD symptoms is responsible for an activation of the CSTC in OCD patients [6]. Finally, at a connectivity level, abnormalities were found in diffusivity as well as volumetric alterations in anterior midline tracts [7–9].

Within the CSTC pathways, the inferior frontal gyrus (IFG) has been implicated as a core region involved in inhibitory control. A recent literature review reports substantial evidence for the involvement of the right IFG (rIFG) in overall inhibitory control (partial or total) in a variety of contexts [10]. Within the rIFG, different sub-regions [pars opercularis (POper); pars orbitalis (POrb); pars triangularis (PTri)] may be involved in various components or modalities of the inhibitory process [11]. There is now also increasing evidence for the involvement of the left IFG (lIFG) in the regulation of inhibitory processes, particularly when overt motor responses are involved [12].

Given the deregulation of inhibitory control in OCD, one may expect brain abnormalities in the bilateral IFG as well as its parcellations. This has been confirmed in a recent multicenter voxel-based morphometry mega-analysis with 412 OCD patients, which reported the existence of low gray and white matter volumes in the bilateral IFG [13]. Decreased activation of the IFG has also been reported with OCD patients during an inhibitory task [14]. However, to the best of our knowledge, no published studies have investigated structural connectivity in the IFG using diffusion tensor imaging (DTI) with OCD patients. Therefore, the main aim of the present study is to examine white matter connectivity in the IFG, as captured by four DTI indices: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). As a secondary objective, the current study aims to assess region-specific white matter connectivity abnormalities by carrying out
an exploratory analysis of DTI indices, independently, for each IFG parcellation (i.e., POper, PORb, PTri).

Methods

Participants
Fifteen patients with OCD (11 men, four women) and 15 nonclinical controls (NCC) (nine men, six women), matched by age and education, were enrolled in the present study. Both patients and controls were right-handed as indexed by the Edinburgh Handedness Inventory (EHI ≥ 80) [15]. OCD patients were diagnosed using the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders [16] and the severity of OCD symptoms was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [17]; depression symptoms were assessed using the Beck Depression Inventory (BDI) [18]. No comorbid conditions were identified in the OCD group. All patients were following treatment-as-usual and were required to be on stable pharmacological treatment (at least 3 weeks of combined antidepressant and anxiolytic medication) and behavioral therapy. The control group did not present a history of drug abuse, psychiatric or neurological disorders, or the use of psychotropic medication. The healthy controls underwent the same assessment as the OCD group. Groups did not differ in age [t (28) = 0.44, P = 0.66] and years of education at the time of the scan [t (28) = -0.35, P = 0.73]. As expected, the Y-BOCS and BDI scores were higher in the clinical group [t (28) = 12.81, P < 0.001; t (28) = 3.60, P = 0.001], respectively. BDI scores were below the cut-off in both groups.

Before the study, all participants provided written informed consent. The study was carried out in accordance with the declaration of Helsinki and was approved by the local review board.

Image data acquisition

Within 1 week of the clinical assessment, participants underwent the scanning procedure in a clinically approved Siemens Magnetom TrioTim 3 T (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. For structural analysis and registration to standard space, a T1 high-resolution anatomical sequence (i.e., 3D magnetization prepared rapid gradient echo) was performed with the following scan parameters: repetition time (TR) = 3.60 ms, echo time (TE) = 93 ms, in-plane resolution = 1 × 1 mm², and slice thickness = 1 mm. The scanning parameters for the DTI acquisition were as follows: 2D echo-planar, voxel size = 2 × 2 × 2 mm³, T2 = 82, TR = 8000; FA = 90; and 64 noncollinear directions with a diffusion gradient of b = 700 s/mm².

Axial T2-weighted images (TR = 6000 ms, TE = 93 ms, slice thickness = 2 mm, voxel size 2 × 2 × 2 mm, flip angle = 120°, FOV = 256 mm) were acquired before DTI acquisition. Diffusion gradients were applied along 64 directions with one b factor = 0 s/mm² and a maximum b factor of 700 s/mm² using a single-shot echo-planar imaging sequence. The diffusion protocol parameters were TR = 8000 ms, TE = 82 ms, slice thickness 2 mm, voxel size 2 × 2 × 2, and flip angle = 90°.

Data preprocessing and analysis

The pipeline for region of interest (ROI) extraction was as follows: (a) reconstruction of the T1-weighted images using the FreeSurfer software; (b) manual corrections using the FreeSurfer pipeline (http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction); and (c) label-map extraction. The IFG and its parcellations (POper, POrb, POPer) were extracted using a White Matter parcellation (wmparc) computed using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu). These ROIs were created by the gyral white matter parcellation. Specifically, this was an entirely ROI-based analysis, in which WM indices are referring only to the voxels inside the ROIs and not to any specific tract. Finally, these ROIs were registered into the DTI native space and the DTI analysis was carried out according to the following steps: (a) Eddy current distortion (DTI Prep); (b). T1 coregistration in DTI (rigid-body transformation, affine transformation, and b-spline transformation); (c) spatial registration of DTI and ROI fiber tracking; and (d) estimation of the FA, MD, RD, and AD parameters with a 3D slicer (http://www.slicer.org). FA is a measure describing the degree of water anisotropy diffusion in the brain. High FA values indicate a diffusion of water molecules along the fiber and are usually seen as synonymous with white matter integrity. In contrast, MD indicates the existence of nonspecific barriers for free diffusion in the fiber. AD is a measure of longitudinal diffusion and seems to be a marker of axonal damage. Finally, RD is a measure of the transverse direction of diffusion and a good marker of altered myelination processes.

Statistical analysis

Independent t-tests were performed to assess white matter diffusion properties (i.e., FA, MD, RD, AD) for each hemisphere. A total of eight independent-sample t-tests were performed. Applying a Bonferroni correction on the basis of eight multiple comparisons, the α for statistical significance was set at up to 0.006. In addition, a secondary exploratory analysis was carried out for each of the IFG parcellations (i.e., POper, PORb, and PTri).

Given the exploratory nature of this secondary analysis, no adjustment was made for multiple comparisons.

Results

Whole IFG

Right hemisphere

When compared with NCC, OCD patients showed significantly lower FA along with higher MD and RD.
No significant differences were found between groups for AD (Fig. 1 and Table 1).

Left hemisphere
For the lIFG, OCD patients showed significantly lower FA, and higher MD and RD compared with NCC. Again, no significant differences were found between groups for AD.

IFG-POper
Right hemisphere
Compared with NCC, OCD patients had significantly lower FA along with higher MD and AD.

Left hemisphere
Significantly lower FA and higher MD and RD were evident in OCD. No differences were found between groups for AD.

IFG-POrb
Right hemisphere
OCD patients had significantly lower FA along with higher RD. No significant differences were found between OCD and NCC for MD and AD.

Left hemisphere
OCD patients had significantly lower FA (compared with NCC). However, no statistically significant differences between groups were found in the remaining diffusion indexes.

IFG-PTri
Right hemisphere
OCD patients had, compared with NCC, significantly lower FA along with higher MD and RD. Once again, no differences were found between groups for AD.

Left hemisphere
Finally, OCD patients had, compared with NCC, significantly lower FA and increased values of MD, RD, and AD.

Discussion
The present study found evidence for abnormal white matter connectivity in patients with OCD compared with healthy matched controls in the bilateral IFG, both as a whole as well as in terms of its parcellations (POper, POrb, PTri). More specifically, for the total IFG, OCD patients had significantly lower FA and correlative increases in MD and RD. No differences were evident in terms of AD. These findings are consistent with previous structural MRI studies showing abnormally low gray and white matter volumes in the inferior frontal cortex for individuals with OCD [7]. Higher levels of MD, along with RD, may suggest the existence of altered myelination (i.e. increased RD) in white matter adjacent to a core brain region implicated in inhibitory control. These findings are consistent with the conclusions of a systematic review and meta-analysis of DTI studies in OCD, showing that higher RD and MD along with no significant changes in AD were evident in several prefrontal regions of the prefrontal cortex [8].

OCD patients suggests a disruption of myelin integrity. Even though the rIFG has been reported as the primary region implicated in response inhibition [10], there is also evidence for the role of the lIFG in the inhibition of overt motor responses [12].

As discussed previously, the prevailing OCD pathophysiological model posits that obsessions and compulsions are symptomatic expressions of impairments in inhibitory processes [2]. Difficulties with inhibitory control seem to underlie difficulties in suppressing and inhibiting not only thoughts but also compulsive overt behaviors [19]. Given the central role played by both the IFG and the rIFG in inhibitory control, the current findings of decreased FA and increased diffusivity levels in regions adjacent to the bilateral IFG lend additional support to the prevailing model of OCD as a disorder of inhibitory control. However, as no comparisons were made with other psychiatry disorders, no definitive conclusions can be made on the specificity of the current findings for OCD. Indeed, deficits in inhibitory control have been reported to be associated with functional and structural alterations of the IFG in other psychiatric conditions such as attention deficit hyperactivity disorder and substance use disorders [20]. In addition, alterations of connectivity have been reported in tracks connecting the inferior frontal cortex with subcortical structures in several anxiety conditions [21]. Typically, OCD patients report clinical significant anxiety. As no comparison was performed with other anxiety conditions, we cannot rule out the hypothesis that anxiety levels may be mediating the connectivity differences between OCD and NCC. Altogether, we may be in presence of alterations transdiagnostic to several clinical conditions. Future studies should address this issue by introducing systematic comparisons between OCD and other disorders inside and outside the OCD spectrum.

When looking at the three parcellations of the IFG, the current study, even though exploratory, found evidence for widespread connectivity abnormalities in all three IFG subregions as evidenced by low levels of FA in POper, POrb, and PTri. These data are consistent with the results of a recent functional MRI study showing that OCD patients, when confronted with emotionally aversive pictures, showed significantly higher activation of the same IFG subregions than matched controls [22]. The diversity of local connectivity from each IFG subregion [23] may explain the current evidence that each parcellation of the IFG is associated with specific components of the inhibitory response [11]. This being the
case, each IFG subregion may play a distinct role in OCD-related deficits with response inhibition [4]. High levels of RD were found in all IFG subregions (except for the left POrb), whereas significant AD alterations were restricted to the right POper and left PTri. This suggests that OCD-related increases in diffusivity could be, at least partially, attributable to demyelination processes (as indexed by RD) rather than axonal damage (as indexed by AD). These data are consistent with previous studies [24,25], which suggest that increased diffusivity in OCD patients may be caused by elevated RD rather than AD.
The present study found evidence for significant alterations in brain connectivity for individuals with OCD, as expressed by low levels of FA and high levels of diffusivity in the whole IFG as well as its parcellations (the POOr, POOr, and PTri). In addition, these alterations seem to impact connectivity in the left and right hemispheres. Finally, whereas differences in RD were widespread through most regions analyzed (except for the left POOr), higher levels of AD were restricted by region (e.g. the right POOr and left PTri). Even though the present study found evidence of white matter abnormality in regions associated with processes of inhibitory control, no direct measures for these processes were indexed. Future studies should correlate white matter connectivity in the IFG and its parcellations with performance in various inhibitory control tasks using a large sample of OCD patients carefully matched with healthy controls and other clinical conditions within and outside the OCD spectrum.

**Conclusion**

The present study found evidence for significant alterations in brain connectivity for individuals with OCD, as expressed by low levels of FA and high levels of diffusivity in the whole IFG as well as its parcellations (the POOr, POOr, and PTri). In addition, these alterations seem to impact connectivity in the left and right hemispheres. Finally, whereas differences in RD were widespread through most regions analyzed (except for the left POOr), higher levels of AD were restricted by region (e.g. the right POOr and left PTri). Even though the present study found evidence of white matter abnormality in regions associated with processes of inhibitory control, no direct measures for these processes were indexed. Future studies should correlate white matter connectivity in the IFG and its parcellations with performance in various inhibitory control tasks using a large sample of OCD patients carefully matched with healthy controls and other clinical conditions within and outside the OCD spectrum.

**Acknowledgements**

O.F.G. designed the study, coordinated data acquisition, and wrote the manuscript. J.L. and S.C. collected data, carried out the statistical analysis, and collaborated in manuscript writing. A.S., L.M., and S.S. preprocessed the data and collaborated in manuscript writing. A.G., A.F.G., and F.P. helped with patient recruitment and psychiatry assessment. B.F. and A.C. collaborated in manuscript writing. All authors read and approved the final manuscript.

This work was partially supported by a research award to the first author (O.F.G.) from the Brain Imaging Network Grid/FCT (Portugal). Jorge Leite (SFRH/BPD/86027/2012) and Sandra Carvalho (SFRH/BPD/86041/2012) are supported by grants from the Portuguese Foundation for Science and Technology (FCT) and European Union (FSE-POPH).

**Conflicts of interest**

There are no conflicts of interest.

**References**


Table 1 Results of t-tests comparisons between OCD and NCC in terms of white matter diffusion properties (i.e. FA, MD, RD, AD) for the IFG and its parcellations in each hemisphere

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<th>Fractal anisotropy</th>
<th>Axial diffusivity</th>
<th>Radial diffusivity</th>
<th>Mean diffusivity</th>
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<td><strong>Whole IFG</strong></td>
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<td>OCD vs. NCC</td>
<td>Right</td>
<td>−4.217</td>
<td>0.001*</td>
<td>1.733</td>
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<td>Left</td>
<td>−3.716</td>
<td>0.001*</td>
<td>2.127</td>
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<td>Left</td>
<td>−3.853</td>
<td>0.001*</td>
<td>3.143</td>
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<td>−1.41</td>
<td>0.004*</td>
<td>1.15</td>
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<td><strong>Hemisphere</strong></td>
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<td><strong>OCD vs. NCC</strong></td>
<td>Right</td>
<td>−3.707</td>
<td>0.001*</td>
<td>0.142</td>
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<td>Left</td>
<td>−2.653</td>
<td>0.013*</td>
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<td><strong>Parcellations</strong></td>
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<td><strong>OCD vs. NCC</strong></td>
<td>Pars opercularis</td>
<td>−3.723</td>
<td>0.001*</td>
<td>1.36</td>
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<td>−1.14</td>
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<tr>
<td><strong>OCD vs. NCC</strong></td>
<td>Pars orbitalis</td>
<td>−3.120</td>
<td>0.004*</td>
<td>2.237</td>
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<td>−1.14</td>
<td>0.034*</td>
<td>0.82</td>
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<td><strong>OCD vs. NCC</strong></td>
<td>Pars triangularis</td>
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AD, axial diffusivity; FA, fractional anisotropy; IFG, inferior frontal gyrus; MD, mean diffusivity; NCC, nonclinical control; OCD, obsessive–compulsive disorder; RD, radial diffusivity.

* <0.006 for the whole IFG (after Bonferroni correction); <0.05 for the remaining parcellations.