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Widespread changes of white matter microstructure in obsessive-compulsive disorder: Effect of drug status

Francesco Benedetti[a,b,*], Chiara Giacosa[a,b,1], Daniele Radaelli[a,b], Sara Poletti[a,b], Elena Pozzi[a,b], Sara Dallaspezia[a,b], Andrea Falini[b,c], Enrico Smeraldi[a,b]

[a]*Department of Clinical Neurosciences, Scientific Institute and University Vita-Salute San Raffaele, Milano, Italy*
[b]*Centro di Eccellenza Risonanza Magnetica ad Alto Campo (C.E.R.M.A.C.), Milano, Italy*
[c]*Department of Neuroradiology, Scientific Institute and University Vita-Salute San Raffaele, Milano, Italy*

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Abstract
Diffusion tensor imaging (DTI) allows the study of white matter (WM) structure. Literature suggests that WM structure could be altered in obsessive-compulsive disorder (OCD) proportional to the severity of the disease. Heterogeneity of brain imaging methods, of the studied samples, and of drug treatments make localization, nature, and severity of the WM abnormalities unclear. We applied Tract-Based Spatial Statistics (TBSS) of DTI measures to compare fractional anisotropy (FA), mean, axial, and radial diffusivity of the WM skeleton in a group of 40 consecutively admitted inpatients affected by severe OCD (18 drug-naive, and 22 with an ongoing drug treatment) and 41 unrelated healthy volunteers from the general population. Data were analyzed accounting for the effects of multiple comparisons, and of age, sex, and education as nuisance covariates. Compared to controls, OCD patients showed a widespread reduction of FA with a concurrent increase of mean and radial diffusivity. In no brain areas patients had higher FA or lower diffusivity values than controls. These differences were observed in drug-treated patients compared to drug-naive patients and healthy controls, which in turn did not differ among themselves in any DTI measure. Reduced FA with increased mean and radial diffusivity suggests significant changes in myelination of WM tracts, without axonal loss. Drug treatments could modify the structure of cell membranes and myelin sheaths by influencing cellular lipogenesis, cholesterol homeostasis, autophagy, oligodendrocyte differentiation and remyelination. Changes of DTI

*Corresponding author at: Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy. Tel.: +39 02 2643 3156; fax: +39 02 2643 3265.
E-mail address: benedetti.francesco@hsr.it (F. Benedetti).
[1]Current affiliation: Department of Psychology, Concordia University, Montreal, Canada.

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measures in drug-treated OCD patients could reflect pathophysiological underpinnings of OCD, or a yet unexplored part of the mechanism of action of drugs.

1. Introduction

Brain imaging and neuropsychological studies of the possible biological underpinnings of obsessive–compulsive disorder (OCD) point toward failures in the cortical control of fronto-striatal neural circuits (Chamberlain et al., 2005; Fineberg et al., 2010), and suggest that the abnormal neuropsychological performances observed in OCD patients could be due to abnormal structure and function of several cortical regions and of basal ganglia. Morphological alterations are paralleled by abnormal functional responses to cognitive tasks (Remijnse et al., 2006; van den Heuvel et al., 2005), and by an increased metabolic activity of basal ganglia which tends to decrease and normalize after successful treatment (El Mansari and Blier, 2006; Linden, 2006). Abnormal activation patterns involve the interactions among the brain structures: recent BOLD fMRI studies of functional connectivity showed either increased connectivity among fronto-striatal structures in resting conditions (Sakai et al., 2010) and in response to tasks that elicit emotional/motivational responses (Stern et al., 2011), or mixed pictures of increased and decreased connectivity among different brain structures (Harrison et al., 2009; Jang et al., 2010; Zhang et al., 2011) or across different tasks (Fitzgerald et al., 2010).

An altered signal communication between brain networks could be associated with changes of white matter (WM) structure. Brain imaging studies hold significant promise for the investigation of WM in OCD, as suggested by the possibility to develop OCD symptoms after white matter lesions (Fontenelle et al., 2009), and by studies showing either decreased (Duran et al., 2009; Koprivova et al., 2009; van den Heuvel et al., 2009) or increased (Atmaca et al., 2010; Park et al., 2011; Togao et al., 2010) WM volumes in psychiatric OCD patients.

The structure of normal appearing WM can be studied with diffusion tensor magnetic resonance imaging (DTI). DTI measures the extension and direction of water diffusivity and provides indices of WM integrity which could be sensitive to the subtle pathological changes associated with psychiatric conditions (Le Bihan, 2003). Given the microscopic structure of WM, in normal conditions the integrity of myelinated axons limits the diffusion of water in directions other than along the axis of the fiber. This tendency to diffuse in one direction as opposed to all others, termed anisotropy, can be estimated through the application of diffusion-sensitizing gradients and the calculation of elements of the diffusion tensor matrix, i.e. the three eigenvalues λ_1, λ_2 and λ_3. Mean diffusivity (MD, average of λ_1, λ_2 and λ_3) is a measure of the average molecular motion, independent of tissue directionality. Studies in WM pathologies involving disruption of myelin sheaths (Horsfield and Jones, 2002) showed that a decrease of the tendency to diffuse along the principal direction (λ_1) of the fiber (axial diffusivity, AD) suggests axonal loss or loss of bundle coherence, while an increase in diffusivity perpendicular to axonal walls (the average of λ_2 and λ_3, radial diffusivity (RD) suggests disrupted myelination (Song et al., 2002). Fractional anisotropy (FA) values range between 0, when water motion is random in all directions, and 1, when the directional selectivity of water motion is maximal. FA can reflect the structure of axonal cell membranes and myelin sheaths, with high FA values in heavily myelinated tracts (Kochunov et al., 2007).

DTI studies in adult OCD patients gave contrasting, albeit statistically significant, results. Fractional anisotropy was reported to be either significantly decreased (Bora et al., 2011; Chiu et al., 2011; Fontenelle et al., 2011; Garibotto et al., 2010; Nakamae et al., 2011; Oh et al., 2011; Saito et al., 2008; Szeszko et al., 2005) or increased (Cannistraro et al., 2007; Li et al., 2011; Nakamae et al., 2008; Yoo et al., 2007; Zarei et al., 2011), or either increased or decreased in different brain areas (Lochner et al., 2012; Menzies et al., 2008) or in subgroups with different symptomatological dimensions (Ha et al., 2009). Surprisingy, opposite effects were detected in the same WM tracts in the different studies. Regions where a reduction of FA was observed included corpus callosum, cingulum bundle, anterior and posterior limb of the internal capsule, anterior thalamic radiation, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and the WM of parietal and superior frontal regions. Regions where FA was found to be increased included corpus callosum, cingulum bundle, anterior and posterior limb of the internal capsule, semioval center, and the WM of parietal regions and superior, middle and medial frontal gyrus.

All these studies, except one performed in drug naïve patients (Yoo et al., 2007), have been performed on mixed samples including together patients who were either currently taking drugs, drug-free, or drug-naïve, and without comparing these conditions. This led us to hypothesize that a possible reason for the failure to reach a shared knowledge about the relationship between OCD and WM structure could be the confounding and overlooked influence of drug status. To precise the extent and the quality, if any, of possible influences of drug status on WM abnormalities in OCD, here we studied the DTI measures of WM structure by means of tract based spatial statistics (TBSS) in two homogeneous samples of patients affected by OCD and either treated with psychotropic drugs, or drug-naïve, and in healthy controls.

2. Experimental procedures

2.1. Sample, treatment and clinical assessment

We studied 40 inpatients (26 males and 14 females) affected by obsessive–compulsive disorder (DSM-IV criteria, SCID-I interview) and consecutively referred to our hospital unit. Eighteen patients were drug-naïve, and 22 were being administered a drug treatment upon clinical need (including sertraline, fluvoxamine, citalopram, paroxetine, clomipramine, risperidone, olanzapine, haloperidol;

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