



Review

Brain circuitries of obsessive compulsive disorder: A systematic review and meta-analysis of diffusion tensor imaging studies



Federica Piras^a, Fabrizio Piras^a, Carlo Caltagirone^{a,b}, Gianfranco Spalletta^{a,*}

^a IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology, Neuropsychiatry Laboratory, Via Ardeatina 306, 00179 Rome, Italy

^b Department of Neuroscience, Tor Vergata University of Rome, Italy

ARTICLE INFO

Article history:

Received 10 August 2013

Received in revised form

27 September 2013

Accepted 19 October 2013

Keywords:

Obsessive compulsive disorder

Connectivity

White matter micro-structure

Diffusion tensor imaging

Fractional anisotropy

Mean diffusivity

Cortico-striato-thalamo-cortical circuitry

Intra-hemispheric bundles

Posterior parietal/occipital cortices

Corpus callosum

ABSTRACT

The potential role of white matter (WM) abnormalities in the pathophysiology of obsessive compulsive disorder (OCD) is substantially unexplored. Apart from alterations in the WM tracts within cortico-striato-thalamo-cortical circuitry, recent theorizations predict the existence of more widespread WM abnormalities. In this paper we systematically reviewed the current diffusion tensor imaging literature in OCD and purposely evaluated the prevalence and functional significance of specific WM tissue changes in the disorder. The relationship between clinical variables (medication status, symptom severity) and WM microstructural changes was also assessed. The reviewed studies are consistent with the existence of microstructural alterations in the fronto-basal pathways targeting the orbitofrontal cortex and the anterior cingulate cortex. Moreover, altered anatomical connectivity between lateral frontal and parietal regions and microstructural abnormalities in intra-hemispheric bundles linking distinctive areas of the prefrontal cortex to posterior parietal and occipital association cortices, are consistently reported. Finally, microstructural abnormalities in the corpus callosum, characterized by decreased connectivity in the rostrum and hyperconnectivity in the genu, are substantiated by a large body of evidence.

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* Corresponding author. Tel.: +39 06 51501575; fax: +39 06 51501575.

E-mail address: g.spalletta@hsantalucia.it (G. Spalletta).

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1. Introduction

With its prevalence rate ranging between one and four percent, obsessive-compulsive disorder (OCD) is the fourth-most-common mental disorder worldwide (Fullana et al., 2009; Leonard et al., 2005). The main clinical manifestations seen in OCD patients are recurrent, intrusive and distressing thoughts (obsessions) and/or repetitive behaviors or mental acts (compulsions), which are executed to avoid anxiety or neutralize obsessions (American Psychiatric Association, 2000). OCD symptoms interfere significantly with subjects' normal routine and patients are often chronically hampered by functional impairments including poor or failed occupational and educational performance (Koran et al., 2010).

Over the last 2 decades, neuroimaging studies have indicated several neurobiological changes underlying the psychological and behavioral deficits of OCD. Evidence from functional and structural magnetic resonance imaging (MRI) and positron emission tomography (PET) has supported the notion that abnormalities in key gray matter (GM) regions, such as the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus and striatum play an important role in its pathophysiology (Graybiel and Rauch, 2000; Menzies et al., 2008a; Saxena and Rauch, 2000). These findings suggest that a dysfunctional cortico-striato-thalamo-cortical circuitry contributes to the pathophysiology of OCD. However, the overall picture is still rather heterogeneous and recent studies employing whole-brain analyses also indicate more distributed neuroimaging alterations in patients with OCD, implicating other brain regions such as parietal cortex, dorsolateral prefrontal cortex (DLPFC) and posterior temporo-parieto-occipital associative areas (Menzies et al., 2008a).

On the other hand, the white matter (WM) tracts connecting the cortical and subcortical regions are relatively unexplored (Yoo et al., 2007). Consistently with current frontostriatal models of OCD pathophysiology, recent studies (Harrison et al., 2009; Stern et al., 2012; Zhang et al., 2011) showed altered functional connectivity among GM matter nodes of the cortico-striato-thalamo-cortical circuitry. Accordingly, there is growing evidence that OCD symptoms may be at least partly underpinned by reduced WM integrity (Douzenis et al., 2009; Fontenelle et al., 2009). Moreover, recent genetic studies in OCD demonstrated a biased transmission of polymorphisms in genes involved in myelination (Stewart et al., 2007; Zai et al., 2004), suggesting the existence of structural abnormalities of myelin in the disorder.

The only published study reviewing the role of WM abnormalities in the pathophysiology of OCD (Fontenelle et al., 2009) suggests the existence of abnormalities in specific WM tracts (e.g. internal capsule (IC), cingulate bundle (CB), and corpus callosum (CC)) and in different brain regions (medial frontal and parietal WM), in the OCD population. These WM abnormalities may be familial (Menzies et al., 2008b) and responsive to serotonin reuptake inhibitor treatment (SSRI) (Fan et al., 2012; Yoo et al., 2007) and vary according to the severity of different symptom dimensions (Ha et al., 2009; Koch et al., 2012).

Recently, diffusion tensor imaging (DTI) (Basser et al., 1994; Pierpaoli et al., 1996) has been used to detect possible microstructural WM abnormalities in OCD patients. Indeed, DTI is sensitive to the diffusion patterns of water molecules and by

measuring the direction and magnitude of restricted tissue water motility (Frodl et al., 2012), the orientation of WM tracts in the brain can be determined (Nobuhara et al., 2006). The commonly used parameters for measuring WM integrity are Fractional Anisotropy (FA), a measure of directionality of water diffusion, and Mean Diffusivity (MD), a measure of the magnitude of diffusion. Decreased FA indicates a loss of water directionality, likely due to a damage in structural organization of the tissue (Schulte et al., 2005), while increased MD is thought to be linked to an enlargement in the extracellular space due to altered cytoarchitecture, suggesting immaturity or degeneration of the tissue (Syková, 2004). For improving the specificity, the directional diffusivities derived from DTI measurements are separated into components parallel, Axial Diffusivity (AD), and perpendicular, Radial Diffusivity (RD), to the WM tract. Decreased AD is associated with axonal injury and dysfunction, whereas increased RD is associated with myelin injury in mouse models of WM injury (Song et al., 2003). The use of multiple DTI measures, such as a combination of FA, MD, RD and/or AD has already been proven to be helpful in understanding the different mechanisms underlying microstructural changes (Di Paola et al., 2010); however, AD and RD have been hardly reported in OCD and 5 out of the 8 studies reviewed by Fontenelle (Fontenelle et al., 2009) examined only FA without looking at other measures.

Given that DTI provides a particular unique piece of microstructural information about WM organization and connectivity, which volumetric measurements cannot convey (since for example, a disorganized WM pathway is not expected to change substantially in volume), we considered essential to review the current DTI literature in OCD. Moreover, given the rapid evolution of methods for the acquisition and analysis of diffusivity measures, an update of the evidence on WM pathways integrity in OCD is of relevance. Indeed, the number of neuroimaging studies in OCD has grown exponentially in recent years, while findings from different investigations may sometimes be difficult to integrate into a coherent picture. Moreover, each method has advantages and drawbacks since region of interest (ROI) studies are affected by a limited and potentially biased inclusion of brain regions (Radua and Mataix-Cols, 2012), while the use of voxels, as in whole brain and in tract based voxel wise analyses, improves the correct localization of potential abnormalities, but is biased toward group differences that are localized in space (Davatzikos, 2004).

Our main aim was to assess the evidence on WM microstructure abnormalities in the disorder, trying to characterize the specific WM tissue changes (i.e. axonal reduced organization or damage vs. abnormalities of myelin integrity) associated with OCD. As different microstructural indices are sensitive to diverse tissue properties, we tried, whenever possible, to interpret data considering the interrelations between complementary measures of WM microstructure. We also purposely analyzed the relationship between clinical variables such as medication status and symptom severity, and WM microstructural changes, in order to determine whether the observed abnormalities should be considered trait or state markers.

Finally, we intentionally evaluated the evidence of WM microstructural changes outside the cortico-striato-thalamo-cortical loop, as to investigate whether OCD pathology involves WM tracts beyond this classically implicated circuit (Menzies et al., 2008a; Piras et al., 2013). In order to synthesize the findings,

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