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Review

Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): A review

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ABSTRACT

This review presents an overview of studies investigating white-matter integrity in patients with obsessive-compulsive disorder (OCD) using diffusion tensor imaging (DTI). There is increasing evidence for white matter alterations in OCD. In adult patients the majority of all studies reported abnormalities in terms of decreased fractional anisotropy (FA) compared to healthy volunteers. Although findings are heterogeneous, the cingulate bundle, the corpus callosum and the anterior limb of the internal capsule are most commonly affected by decreased white matter integrity in adult OCD patients. In pediatric and adolescent patients initial evidence points more towards increased white matter connectivity. Thus, current results suggest alterations in various white matter regions in both pediatric and adult OCD patients. They indicate that alterations may vary as a function of clinical characteristics and may be amenable to pharmacologic treatment. Although the findings have important implications for the neurobiology of OCD they also raise a number of important questions that are discussed in this review and need to be taken into consideration in future studies.

1. Objectives of the study and background

1.1. Clinical characteristics of OCD

Obsessive-compulsive disorder (OCD) is characterized by recurrent, persistent, and intrusive thoughts or images that cause distress or anxiety (i.e., obsessions), and repetitive behaviors aimed at reducing this feeling of anxiety (i.e., compulsions). Patients may suffer from only obsessions, only compulsion or both obsessions and compulsions (Zaudig, 2011). Compulsions include excessive cleaning or washing, repeated checking, or extreme hoarding; obsessions comprise preoccupation with religious, sexual or violent thoughts, relationship-related obsessions or obsessions related to particular numbers. Importantly, obsessions and compulsions are ego-dystonic, i.e., patients recognize that their thoughts are unreasonable and that they represent products of their own mind (APA, 2000). Clinically, patients differ considerably with regard to symptom type, symptom severity, comorbidity and age of onset (Weissman et al., 1994). As discussed below, this clinical heterogeneity may complicate the identification of general and specific brain regions and networks which are involved in the pathogenesis of the disorder.

1.2. Neurobiology of OCD

The investigation of the neural circuitry involved in OCD has made substantial progress in the last couple of years. Functional neuroimaging methods have helped to identify altered activity within a predominantly fronto-striato-thalamo-cortical circuitry in patients with OCD (Menzies et al., 2008a). This circuitry originates in prefrontal cortex, has connections to the striatum which connects to the globus pallidus and substantia nigra and from there connects to the thalamus. The thalamus finally provides the link back to the frontal cortex. Amongst the frontal regions, the

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dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) seem to be of major psychopathological relevance in OCD (Chamberlain et al., 2008; Evans et al., 2004; Fineberg et al., 2010; Menzies et al., 2008a; O'Neill et al., 2013). According to a frequently discussed model by Saxena and Rauch (2000) excessive activity within frontal subcortical circuits might underlie the repetitive behavior and cognitive inflexibility which characterizes the disorder of OCD (Veale et al., 1996). Here, enhanced activity of the ACC may reflect the increased error-sensitivity and behavioral monitoring in patients with OCD. Thus, individuals with OCD may perform their repetitive, compulsive behaviors as they experience large and persistent error signals (i.e., also called "not just right experience") that manifest emotionally as feelings of wrongness. Compulsive behaviors thus may represent attempts to reduce the perceived discrepancy between preferred and experienced internal states. However, this "not just right experience" remains relatively unaffected by behavior given continued ACC hyperactivity. As a result, individuals with OCD experience persistent feelings of doubts and anxiety and the urge to engage in behaviors to counteract these emotions.

Results of structural studies investigating gray matter structure or volume are partly in line with these models. One meta-analysis identified increased regional gray matter in the basal ganglia and decreased gray matter volumes in the frontal/anterior cingulate gyri as core alterations in OCD (Radua and Mataix-Cols, 2009) while another, very recent meta-analysis, identified, apart from the "classical" fronto-striatal alterations, volume decreases in dorsomedial, ventrolateral and frontopolar prefrontal cortices and connected regions like temporo-parieto-occipital associative areas as well as volume increases in the internal capsule (Piras et al., 2013). Apart from alterations in gray matter volume and structure there is mounting evidence for alterations in white matter fiber tracts in OCD as demonstrated by an increasing number of studies using the method of diffusion tensor imaging (DTI).

1.3. The method of DTI to investigate alterations in white matter structure

DTI is a comparatively young imaging method that permits the quantification of the diffusion characteristics of water molecules in vivo. Within cerebral white matter, water molecules diffuse more freely along myelinated tracts than across them. Such directional dependence of diffusivity is called "anisotropy," and any reduction in white matter anisotropy indicates an alteration in the degree of tissue order or integrity. The reduction may reflect changes to the underlying white matter tracts, including changes in fibers packing, fiber diameter, thickness of the myelin sheaths, and directionality of the fibers. Technically, diffusion is encoded in the MRI signal by magnetic field gradient pulses. Because diffusion can only be detected in the direction of the particular gradient the number of gradient or diffusion encoding directions is a critical parameter in DTI that strongly determines signal strength.

There are different parameters that can be assessed to characterize diffusion or, indirectly, fiber tract characteristics. The most commonly used parameter is fractional anisotropy (FA) which describes the fraction of the magnitude of the tensor that can be ascribed to the anisotropic diffusion and is calculated from the three eigenvalues of the diffusion tensor. Axial diffusivity (AD), also called longitudinal or parallel diffusivity, describes the diffusivity along the principal axis whereas radial diffusivity (RD), usually calculated by averaging the diffusivities in the two minor axes, describes the diffusivity perpendicular to the structure. Studies in shiverer mice have shown that AD may indicate axonal loss, while increased RD may reflect a decrease in myelination (Song et al., 2002). In addition, some studies investigated diffusivity along the single principal diffusion directions (PDD) or mean diffusivity (MD), i.e., the average diffusion along the three major directions calculated as the mean of the three eigenvalues also called apparent diffusion coefficient (ADC). In an attempt to optimize the assessment of white matter microstructure a number of different analysis techniques have been developed. The most frequently used approach is the voxel-wise or voxel-based analysis of diffusion data. With this approach, diffusion data (e.g., FA maps) are coregistered to a high resolution image, spatially normalized and smoothed before statistical tests are performed for each voxel. Consequently, its results are strongly dependent on several parameter settings like, e.g., method of coregistration or size of the smoothing filter (Jones et al., 2005). Another, more recent and increasingly popular method is a tract-based approach as, for instance, implemented in FSL (i.e., tract-based spatial statistics, TBSS) (Smith et al., 2006). Here, individual subjects' FA data are projected into a common space in a way that does not require perfect nonlinear registration. Strictly speaking, this method is likewise voxel-based, but as only regions containing white matter tracts of the brain are analyzed, the term tract-based analysis prevailed. As no spatial smoothing is necessary this method overcomes a number of drawbacks going along with classical voxel-based methods. Today, most DTI studies in patients with OCD applied voxel- or tract-based methods to investigate potential alterations in white matter microstructure in OCD. The current review intended to provide an overview of DTI studies in patients with OCD. Adolescent and adult patients differ in clinical parameters (such as duration of illness or long-term pharmacological treatment) that are known to have a relevant effect on white matter structure. They also vary with regard to the developmental stage of white matter or myelination which is still developing in adolescent patients. Therefore, results are presented separately for adolescents and adults to highlight potential differences in structural alterations between different patient groups or disease stages.

2. Materials and methods

We used PubMed to identify original, English-language, studies that investigated white-matter integrity in patients with OCD applying the method of DTI. Studies were retrieved by using the search terms "obsessive-compulsive" and "diffusion tensor imaging" or "DTI". We included only studies involving patients with a DSM-IV diagnosis of OCD (i.e., not included were den Braber et al., 2011; Kochunov et al., 2010; Makki et al., 2009; Neuner et al., 2010; Simmons et al., 2012), and excluded studies based on patients only (Koch et al., 2012). Moreover, we excluded ROI analyses (Cannistraro et al., 2007; Chiu et al., 2011; Lochner et al., 2012; Lopez et al., 2013; Oh et al., 2012; Saito et al., 2008) as they investigate specific regions only and would distort the overall picture.

The majority of all DTI studies investigated white matter alterations in adult OCD patients using voxel-based methods as described above (although some of them differed in a number of methodological aspects such as, e.g., method of coregistration). Most of these studies included both male and female patients with patients' mean age ranging between 23 and 39 years and their mean duration of illness ranging between 5 and 19 years (Tables 1 and 2). Up to now, there are only four DTI studies on pediatric or adolescent OCD samples. In these studies patients' mean age varied between 13 and 17 years and their mean duration of illness ranged between 1 and 5 years (Tables 1and 2). Most of all adolescent and adult patients were medicated with selective serotonin reuptake inhibitors (SSRI). The majority of all studies used voxel-based analysis methods with FA as the main outcome parameter (Table 3).

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