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Fronto-limbic microstructure and structural connectivity in remission from major depression

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ABSTRACT

Previous research has suggested that abnormalities within the amygdala and prefrontal cortex (PFC) may underlie major depressive disorder (MDD). The contribution of microstructural alterations within these regions in adult MDD is still equivocal. Therefore, seventeen middle-aged medication-free remitted MDD patients and 21 matched never-depressed control subjects underwent structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). Despite comparable amygdala volumes, remitted MDD patients revealed decreased mean diffusivity (MD) and increased fractional anisotropy (FA) within the left amygdala, which may be interpreted as greater cell density and increased number of fibers, respectively. This last notion was supported by probabilistic tractography results, which revealed increased connectivity from the left amygdala to the hippocampus, the cerebellum and the brain stem. Further, altered microstructure as indicated by increased MD possibly reflecting decreased cell density within the medial PFC (mPFC) was found. Taken together, the current DTI study shows that abnormal microstructure and connectivity of the amygdala and mPFC might be key factors in the pathophysiology of MDD that may account for functional changes.

1. Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder and one of the leading causes of disability worldwide (e.g., WHO, 2001). Besides depressed mood, MDD is characterized by motivational and cognitive impairments. Regarding possible neural circuitry involved in the onset and maintenance of MDD, dysregulation of frontal-subcortical and especially frontolimbic circuits have been put forward to account for both affective and cognitive symptoms (Lee et al., 2008; Phillips et al., 2003b; Seminowicz et al., 2004). In particular interactions between the medial temporal lobe (MTL) and the prefrontal cortex (PFC) appear to be of importance since they are critically involved in the neural circuit mediating emotion perception and mood regulation (Drevets, 1999; Phillips et al., 2003b; Seminowicz et al., 2004). The medial temporal lobe (MTL) and prefrontal cortex seem to be altered both functionally and structurally in depression (Drevets, 1999; Murray et al., 2011; Phillips et al., 2003b). In particular, elevated volume and activity of the amygdala (even during rest) have been reported as key factors in the pathogenesis of MDD (Drevets, 1999; van Eijndhoven et al., 2011, 2009). Normalization of the amygdala hyperactivity has been reported during successful antidepressive drug treatment and its persistence during remission with higher risk of depressive relapse (Drevets, 1999). The orbito and medial prefrontal cortical areas (OFC, mPFC) have been found to show structural impairments, like reduced gray matter volume and gial cell reduction in MDD. Those and other prefrontal regions like the dorsolateral PFC (dlPFC) showed hyperactivity in MDD (Drevets, 1999). The PFC and the amygdala are excessively linked with each other and jointly regulate processing of emotional material (Phillips et al., 2003a). For emotional memory processing the amygdala mediates memory operations in other regions, including the hippocampus and prefrontal cortex (LaBar and Cabeza, 2006). The dysfunction of the PFC areas might functionally impair the modulation of the amygdala, causing altered emotional processing (Drevets, 1999) and might be associated with negative memory biases in MDD.

Abnormalities in white matter (WM) may be especially relevant for the dysfunctional interaction between frontal and subcortical structures (Sexton et al., 2009). In vivo, WM microstructural integrity

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can be investigated by means of diffusion tensor imaging (DTI). DTI is a unique MR imaging modality that probes the diffusion profiles of water molecules on the micrometer scale. Two scalar measures are often compared over populations using voxel-wise whole brain or region-of-interest (ROI) statistics: mean diffusivity (MD) provides a measure of diffusion and can be used as a marker of cell or fiber density while fractional anisotropy (FA) measures integrity of WM fibers and the amount of directionality (Basser, 1995; Jones, 2008). Often, DTI is seen as a technique suited for investigation of WM integrity, yet alterations within gray matter can also be detected with DTI, as for example within the thalamus (Behrens et al., 2003a, 2003b) or amygdala (Solano-Castiella et al., 2009; Tomasino et al., 2011). Therefore, DTI might provide a valuable strategy for in vivo detection of subtle structural deviations within the amygdala that cannot be visualized by conventional imaging methods (Basser and Jones, 2002; Taylor et al., 2004a).

To be able to investigate not only the amount of directionality but estimate the direction of fiber orientation and investigate anatomical connectivity, additional diffusion tractography analyses have to be conducted. By tracking the principal diffusion direction from voxel to voxel, tractography methods can reconstruct the most probable white matter pathways in vivo (Mori and van Zijl, 2002). Probabilistic tractography produces a global probability density map where the value of each voxel presents the confidence that that voxel is part of the connectional pathway that originates from the seed ROI (Nucifora et al., 2007). Probabilistic tractography has been shown to be especially useful to trace pathways not only in white but also in grey matter (Behrens et al., 2003b; Parker et al., 2003) and therefore has been used in this study.

Thus far, the majority of DTI studies in MDD have focused on late-life or geriatric depression and found diverse microstructural alterations (Alexopoulos et al., 1997; Baldwin and O'Brien, 2002; Dalby et al., 2010; Greenstein et al., 2010; Sexton et al., 2009; Taylor et al., 2007a, 2008, 2007b, 2004b; Yang et al., 2007; Yuan et al., 2007). Due to aging processes influencing both the healthy and depressed brain it is not expected though that results from late-life depression research can be generalized to middle-aged MDD, especially with respect to WM differences. Given that WM is still in development in adolescence (Barnea-Goraly et al., 2005), results from those studies can probably also not be generalized to depression in adulthood (Hulvershorn et al., 2011).

DTI studies in young or middle-aged patients with MDD, however, are still scarce. Though, Li et al. (2007) investigated adult patients, focused exclusively on prefrontal connectivity and found lower FA values bilaterally in prefrontal WM. Two other studies investigating treatment-naïve first episode MDD patients (Ma et al., 2007; Zhu et al., 2011) suggest that WM abnormalities may be present early in the course of MDD and that they may disrupt emotional mood circuits. In addition, Abe and colleagues (2010) used a whole brain approach, found increased MD and interpreted it as reduced cellular density in depressive patients in mediotemporal regions, pons, cerebellum, bilateral frontal and temporal lobes in the absence of any difference in FA. A tract-based spatial statistic (TBSS) study showed a trend towards decreased FA in middle-aged MDD patients within the right cingulate cortex, posterior body of corpus callosum and the sagittal stratum, a prominent WM fiber bundle connecting the occipital lobe to the rest of the brain (Kieseppa et al., 2010). Taken together the results in adult MDD patients, decreased FA in white matter have been reported early in the course of MDD, suggesting impaired anatomical connectivity. Reports on altered MD values and increased FA values are scarce.

None of the studies in middle-aged MDD investigated a drug-free sample in remission focusing on amygdala-frontal microstructure and connectivity. However, microstructural changes present during remission from depression might be mood-independent markers, either for a preexisting vulnerability or comparable to a neuronal 'scar', caused by previous major depressive episodes (MDE). Thus, structural abnormalities during remission from MDD might represent potential risk factors for depressive symptoms to (re)occur. Investigating pharmacological effects might be of independent interest; they however might mask disorder effects, which are the focus of the study at hand.

We therefore set out to measure microstructural integrity and investigate WM connectivity in medication-free middle-aged patients remitted from MDD. We performed an exploratory whole-brain analysis and additional hypothesis driven ROI analyses. Based on the known involvement of the fronto-limbic circuit in MDD as described beforehand, we used MTL and prefrontal regions as ROIs. Regions revealing altered microstructure were used as seed regions for probabilistic tractography. To control for potential confounds of differences in subcortical volumes, volumetric measures were included. Therefore, this is the first study in unipolar MDD, combining diffusion tensor FA and MD measures, probabilistic tractography and structural volumetric analysis in middle-aged patients remitted from MDD without confounding drug usage. Abnormalities in absence from clinical symptoms would suggest that microstructural changes may play a key role in the pathophysiology of MDD and deserve special attention in understanding depressive relapses.

2. Methods

2.1. Participants

Seventeen medication-free remitted major depressive disorder (MDD) patients (4 male, aged between 21 and 51 years, mean age = 30.4 years) and 21 healthy volunteers (7 male, aged between 18 and 45 years, mean age = 26.9 years) participated in this study. There were no significant group differences in age or gender distribution (minimum $p = .27$).

For an overview of participants characteristics see Table 1. All participants were right-handed, physically healthy and did not use any medication. Exclusion criteria were a history of severe somatic diseases, current or past alcohol or substance abuse or dependency, current psychotropic drug use, and postmenopausal phase. Pregnancy, claustrophobia, and metal implants were MR exclusion criteria. Participants with psychiatric diagnoses other than MDD as assessed with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) were excluded. MDD diagnoses were established by use of the revised Structural Clinical Interview for DSM (SCID-I; mood section) (First et al., 1996). All patients did meet criteria for one to three prior MDEs. Inclusion criteria for the healthy control group (HC) were no lifetime DSM-IV Axis-I disorder as assessed with the MINI, and no history of psychiatric disorders in first-degree relatives. We established this last criterion to minimize heritable trait effects in the control group that might confound comparisons with our remitted MDD group. The study protocol was approved by the local ethical committee (CMO region Arnhem-Nijmegen, The Netherlands). All participants gave written informed consent prior to participation.

2.2. Neuropsychological assessments

We assessed psychopathology by a clinical interview, as well as by the MINI, the mood section of the SCID, the Hamilton Depression Scale (HDRS) (Hamilton, 1960), and the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). Handedness was tested with the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). A standard neuropsychological test battery was administered to compare neuropsychological functions between