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Research report

White matter microstructure alterations of the medial forebrain bundle in melancholic depression

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ABSTRACT

Background: The medial forebrain bundle (MFB) is a key structure of the reward system and connects the ventral tegmental area (VTA) with the nucleus accumbens (NAcc), the medial and lateral orbitofrontal cortex (mOFC, lOFC) and the dorsolateral prefrontal cortex (dlPFC). Previous diffusion tensor imaging (DTI) studies in major depressive disorder point to white matter alterations of regions which may be incorporated in the MFB. Therefore, it was the aim of our study to probe white matter integrity of the MFB using a DTI-based probabilistic fibre tracking approach.

Methods: 22 patients with major depressive disorder (MDD) (12 melancholic-MDD patients, 10 non-melancholic-MDD patients) and 21 healthy controls underwent DTI scans. We used a bilateral probabilistic fibre tracking approach to extract pathways between the VTA and NACC, mOFC, lOFC, dlPFC respectively. Mean fractional anisotropy (FA) values were used to compare structural connectivity between groups.

Results: Mean-FA did not differ between healthy controls and all MDD patients. Compared to healthy controls melancholic MDD-patients had reduced mean-FA in right VTA-lOFC and VTA-dlPFC connections. Furthermore, melancholic-MDD patients had lower mean-FA than non-melancholic MDD-patients in the right VTA-lOFC connection. Mean-FA of these pathways correlated negatively with depression scale rating scores.

Limitations: Due to the small sample size and heterogeneous age group comparisons between melancholic and non-melancholic MDD-patients should be regarded as preliminary.

Conclusions: Our results suggest that the melancholic subtype of MDD is characterized by white matter microstructure alterations of the MFB. White matter microstructure is associated with both depression severity and anhedonia.

1. Introduction

Anhedonia, the loss of previously rewarding experiences is a core feature of major depressive disorder (MDD) and may underlie a dysfunction of the reward system, which mediates feelings of pleasure and is essential for motivated behaviour (Haber and Knutson, 2010; Keedwell et al., 2005; Wacker et al., 2009). Core regions of the reward system include the ventral tegmental area (VTA), the nucleus accumbens (NAcc), the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (dlPFC) (Haber and Knutson, 2010). Previous functional magnetic resonance imaging (fMRI) studies have repeatedly demonstrated alterations of the medial forebrain bundle in major depressive disorder (MDD) when processing rewarding stimuli. For instance, in patients with MDD the blood oxygenation level dependent (BOLD) response of the NAcc and the caudate nucleus is less responsive to monetary reward (Pizzagalli et al., 2009) which has been shown to normalize after successful antidepressive therapy (Stoy et al., 2012).

The medial forebrain bundle (MFB) connects above mentioned brain regions and may contribute to reduced motivation and anhedonia in MDD (Schultz et al., 1997; Tye et al., 2013). Using Diffusion Tensor Imaging (DTI) based tractography the MFB was

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first reconstructed by Coenen et al. (2009) in patients with Parkinson's disease. Coenen et al. (2009, 2012) described two different branches of the MFB. An infero-medial branch (imMFB) connects the VTA with the hypothalamus and the NAcc and corresponds to the classical description in rodents. In addition a supero-lateral branch (slMFB) was identified showing far reaching connections to frontal lobe structures including the OFC and the dlPFC. A recent DTI fibre tracking study reconstructed the slMFB and used these fibre tracts as targets for deep brain stimulation (DBS) in treatment resistant depression yielding promising treatment responses (Schlaepfer et al., 2013).

Previous DTI-studies probing white matter integrity in MDD described alterations of brain regions that may be part of the MFB. For instance, increases of FA in the VTA and decreases of FA in the dlPFC were reported using region of interest (ROI) approaches (Bae et al., 2006; Blood et al., 2010). Using tract-based spatial statistics (Korgaonkar et al., 2011) detected reductions of FA in the dlPFC in melancholic but not in non-melancholic MDD patients. Furthermore, alterations of white matter integrity of the anterior limb of the internal capsule were found in MDD (Zhu et al., 2011; Zuo et al., 2012), a region where many pathways mingle, amongst others the MFB and the anterior thalamic radiation which are difficult to disentangle using DTI-based methods (Gutman et al., 2009; Schoene-Bake et al., 2010). One group (Blood et al., 2010) applied a ROI approach and identified a trend for reduced FA in the imMFB which did not reach significance.

However, despite increasing evidence for white matter alterations in MDD (Blood et al., 2010; Keedwell et al., 2012; Liao et al., 2013), and the central importance of the MFB for reward processing (Coenen et al., 2012); to date no DTI fibre tracking study specifically investigated white matter microstructure of the MFB in MDD. DTI fibre tracking is a more sensitive approach than voxel-based methods to identify hypothesis driven white matter alterations of specific pathways (Kanaan et al., 2006; Keedwell et al., 2012). Therefore, in our study we used a bilateral probabilistic fibre tracking approach (Bracht et al., 2013; Kreher et al., 2008; Saur et al., 2008) in order to reconstruct specific segments of the MFB connecting VTA, NAcc, mOFC, lOFC and dlPFC.

One potential confound in study design in MDD leading to inconsistent results may be differences in clinical presentations (Liao et al., 2013; Rush, 2007), which warrants investigation of more homogenous subgroups such as the melancholic subtype (Baeken et al., 2010; Linden et al., 2011). The melancholic subtype is characterised by the presence of anhedonia, difficulties to initiate movements and psychomotor retardation (Rush and Weissenburger, 1994; Winograd-Gurvich et al., 2006). Those symptoms are most likely related to the reward system (Haber and Knutson, 2010). Furthermore, functional and structural neuroimaging studies point to specific brain changes in the melancholic subtype in the dlPFC and ACC, core regions of the reward system (Korgaonkar et al., 2011; Pizzagalli et al., 2004). However, the contribution of the MFB to melancholic symptoms of depression still remains to be elucidated. Therefore, we first compared white matter microstructure of healthy controls with all MDD patients. Second, we separately compared healthy controls melancholic and non-melancholic MDD patients. We hypothesized reduced FA in pathways of the reward system in MDD (Liao et al., 2013). Based on previous findings (Korgaonkar et al., 2011; Pizzagalli et al., 2004) and given that core symptoms of the melancholic subtype such as anhedonia are related to the reward system (Parker et al., 1995; Pizzagalli et al., 2004; Rush and Weissenburger, 1994), we expected alterations of white matter properties to be more pronounced in the melancholic MDD group. To enhance specificity of potential findings we reconstructed the optic radiation as a control tract, where we did not expect any alterations of white matter microstructure.

2. Methods

2.1. Subjects

Participants were recruited from the University Hospital of Psychiatry, Bern, Switzerland. Diagnoses were given according to DSM-IV by experienced psychiatrists after clinical interview and review of case files. We performed the structured clinical interview for DSM-IV part 2 (SCID-II) to exclude comorbid personality disorders. Furthermore participants with a history of significant head trauma, electroconvulsive therapy, substance abuse or dependence other than nicotine were excluded from the study. Controls with a lifetime history of depressive episodes or first-degree relatives with any affective disorder were excluded. All participants were right handed. Based on the Hamilton subscale for endogenomorphic depression (HES) patients were classified in melancholic (HES $>=10$) and non-melancholic depressed patients (HES <10) (Thase et al., 1983; Zimmerman et al., 1986). The HES is a sum score of items of the Hamilton depression rating scale (HAMD) (Hamilton, 1967) (middle insomnia, late insomnia, work and activities, retardation, agitation, loss of weight, diurnal variation, hopelessness). Detailed demographics of our sample are given in Table 1. A proportion of participants participated in previous studies investigating psychomotor retardation (Bracht et al., 2012; Walther et al., 2010, 2012). The study protocol was approved by the local ethics committee (KEK-BE 196/09) and was in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.1.1. Comparison of sample characteristics between the melancholic and the non-melancholic subtype

Melancholic and non-melancholic patients did not differ with respect to gender ($p=0.67$), years of education ($p=0.64$), body mass index ($p=0.60$), smoking status ($p=0.56$), activity level ($p=0.24$) and number of episodes ($p=0.85$). There was a trend for melancholic-MDD patients being older than non-melancholic patients ($p=0.053$). Groups did not differ in the Beck-depression inventory (BDI) scores ($p=0.50$) (Beck et al., 1961), but the melancholic subgroup had significantly higher MADRS ($p=0.006$) (Montgomery and Asberg, 1979) and HAMD total scores ($p=0.001$). The HES sum score was higher in the melancholic subgroup ($p<0.001$).

2.2. Data acquisition

2.2.1. MRI acquisition

All images were acquired with a 12-channel signal reception head coil on a 3-Tesla MR scanner (Siemens Magnetom Trio, Erlangen, Germany). High-resolution T1-weighted MR images were obtained using a 3D Modified Driven Equilibrium Fourier Transform (MDEFT) sequence (Deichmann et al., 2004). The optimized acquisition parameters were as follows: 176 sagittal slices, 256×224 matrix (with a non-cubic field of view (FOV) of 256×224 mm, yielding a nominal isotropic resolution of 1 mm^3), 7.92 ms repetition time (TR), 2.48 ms echo time (TE), 16° flip angle, inversion with symmetric timing (inversion time 910 ms), fat saturation and a 12 min total acquisition time. Identical prescription of MR images was achieved using the Siemens Autoalign sequence, which automatically sets up consistent slice orientation based on a standard MRI atlas.

2.2.2. Diffusion tensor imaging (DTI)

For DTI measurements, we used a spin-echo echo-planar-imaging (EPI) sequence (55 slices, FOV $=256\times256$ mm^2, sampled on a 128×128 matrix resulting in 2 mm^3 voxel size, TR/TE $=6000/78$ ms) covering the whole brain (40 mT/m gradient, 5/8 partial Fourier, no acceleration factor, bandwidth 1346 Hz/Px). Diffusion-weighted images (DWI) were positioned in the axial plane parallel