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Research paper

White matter abnormalities in the fornix are linked to cognitive performance in SZ but not in BD disorder: An exploratory analysis with DTI deterministic tractography

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ABSTRACT

Background: In psychosis, white matter (WM) microstructural changes have been detected previously; however, direct comparisons of findings between bipolar (BD) and schizophrenia (SZ) patients are scarce. In this study, we employed deterministic tractography to reconstruct WM tracts in BD and SZ patients.
Methods: Diffusion tensor imaging (DTI) data was carried out with n=32 euthymic BD type I patients, n=26 SZ patients and 30 matched healthy controls. Deterministic tractography using multiple indices of diffusion (fractional anisotropy (FA), tract volume (Vol), tract length (Le) and number of tracts (NofT)) were obtained from the fornix, the cingulum, the anterior thalamic radiation, and the corpus callosum bilaterally.
Results: We showed widespread WM microstructural changes in SZ, and changes in the corpus callosum, the left cingulum and the fornix in BD. Fornix fiber tracking scores were associated with cognitive performance in SZ, and with age and age at disease onset in the BD patient group.
Limitations: Although the influence of psychopharmacological drugs as biasing variables on morphological alterations has been discussed for SZ and BD, we did not observe a clear influence of drug exposure on our findings.
Conclusions: These results confirm the assumption that SZ patients have more severe WM changes than BD patients. The findings also suggest a major role of WM changes in the fornix as important fronto-limbic connections in the etiology of cognitive symptoms in SZ, but not in BD.

1. Introduction

The last two decades have witnessed a large development of non-invasive techniques approaching structural brain changes with new frameworks for studying the cerebral activity (Hagmann et al., 2012). In psychiatry, potential morphological abnormalities have been assessed using voxel-based morphometry (VBM) for density or volume and diffusion tensor imaging (DTI) for white matter (WM) microstructure. However, previous DTI techniques are limited to identify crossing fibers (Emsell et al., 2013) or in localizing alterations to specific tracts (i.e., fornix bundles) (McIntosh et al., 2005). In order to overcome these limitations, a newer method, the DTI-tractography, has been developed and applied in a variety of psychiatric disorders (Behrens and Jbabdi, 2009). This approach allows a *non-invasive* three-dimensional visualization and in vivo identification of fiber tracts (Basser et al., 2000), thus enabling the white matter (WM) bundle reconstruction typically found in post mortem analysis (Catani et al., 2002a). DTI tractography is based on the likelihood of fiber connectivity

List of abbreviations: BD, bipolar disorder; DTI, diffusion tensor imaging; FA, fractional anisotropy; Vol, tract volume; Le, tract length; NofT, number of tracts; VBM, voxel based morphometry; WM, white matter; MD, mean diffusivity; CC, corpus callosum; SCID, Structured Clinical Interview for the DSM IV; BDI II, Beck Depression Inventory; BRMAS, Bech Rafaelsen Mania Scale; MWT-B, Mehrfach-wahl-Wortschatz-Test; TMT, Trail Making Test; EPI, echo planar imaging; ATR, anterior thalamic radiation; F, Fornix; C, Cingulum

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between voxels and the preferred water movement (diffusion) in the surrounding voxels (Mori and van Zijl, 2002). The technique may be either global or local, probabilistic or deterministic (Behrens and Jbabdi, 2009). Probabilistic tractography requires a model of the uncertainty of each fiber orientation estimate (Seunarine and Alexander, 2009). Conversely, deterministic tractography relies on the streamline tractography principles to exploit multiple fibers in each voxel (Behrens and Jbabdi, 2009; Catani et al., 2002) and has been successfully deployed to isolate and visualized many different WM pathways (Behrens and Jbabdi, 2009).

One major goal of recent structural imaging studies is to identify similarities and differences in neural mechanisms of bipolar disorder (BD) and schizophrenia (SZ) in order to improve our understanding of the pathophysiological basis of the clinical continuum of psychosis (Craddock et al., 2006). Current knowledge suggest that BD and SZ patients share neuropsychological deficits (Hill et al., 2013) both in pharmacological response (Murray et al., 2004) and genetic susceptibility (Craddock et al., 2006).

Microstructural integrity loss in various WM fiber tracts in BD have been reported by several groups using DTI (Emsell and McDonald, 2009; Vederine et al., 2011). Multimodal networks may be disrupted by WM microstructure changes, namely the thalamo-fronto-striatal and fronto-temporal connections (Adler et al., 2005; Sussmann et al., 2009). Findings in BD are heterogeneous regarding the direction of diffusion changes. In fact, while most investigations have reported fractional anisotropy (FA) reductions (Benedetti et al., 2011a; Chaddock et al., 2009; Lu et al., 2011; Macritchie et al., 2010) a smaller amount of studies have noted FA increases compared to healthy controls (Versace et al., 2008; Wessa et al., 2009). To the best of our knowledge, there are scarce studies carried out with DTI tractography in BD samples (Barysheva et al., 2013; Emsell et al., 2013; Lin and al, 2010; Sarrazin et al., 2014; Toteja et al., 2014). One tractography investigation observed lower FA and higher mean diffusivity (MD) in the corpus callosum (CC) (i.e., genu, splenium) and also in both projection and association fibers. MD changes were associated with age in the genu and splenium of the corpus callosum (Toteja et al., 2014). In another study, decreased FA in the anterior thalamic radiation and uncinate fasciculus were reported (Lin and al, 2010). However, the fornix WM microstructure was less frequently examined. The existing results showed no major structural changes in this region in BD compared with controls (al., 2008; Barysheva et al., 2013).

Accordingly, a recent meta-analysis (Williamson and Allman, 2012) of diffusion tensor imaging (DTI)-studies in SZ compared with controls yielded two regions with significant WM changes: the left frontal deep WM and the left temporal deep WM. DTI tractography studies revealed abnormalities in WM integrity in several structures, e.g. the fornix (Abdul-Rahman et al., 2011; Fitzsimmons et al., 2009; Kuroki et al., 2006).

Regarding the functional relevance of these findings, WM alterations may arguably underscore'hot' and 'cold' cognitive deficits in psychosis. This assumption has been supported by emerging findings that point to a relationship between WM changes and cognitive dysfunction in BD as well as in SZ (Bauer et al., 2015; Ehrlich et al., 2011; Gutierrez-Galve et al., 2011; Hartberg et al., 2010, 2011; Knochel et al., submitted,; Knochel et al., 2014; Oertel-Knochel et al., 2012, 2014; Poletti et al., 2015; Bauer et al., 2015; Poletti 2015; Kafantaris et al., 2009). Notwithstanding some findings of state-dependent changes in WM integrity have been reported (e.g. Sussmann et al., 2009; Versace et al., 2008; Zanetti et al., 2009), most studies point towards trait-like WM alterations that are independent of current affective symptoms (Chaddock et al., 2009; Haller et al., 2011; Oertel-Knochel et al., 2014; Wessa et al., 2009; Yurgelun-Todd et al., 2007).

Studies investigating DTI-based changes in SZ and BD patients are rare; four studies exist (McIntosh et al., 2008; Sussmann et al., 2009; Lu et al., 2011; Cui et al., 2011) but have examined samples that differ in important respects. Additionally, to the best of our knowledge, none of the existing studies addressed DTI tractography to SZ and BD patients in one study. Therefore we used deterministic tractography, a straightforward method to compare fiber-tracking scores of various tracts in participants with BD and SZ compared to age- and gender-matched healthy controls. A further goal of the current study was to identify potential associations between affective or cognitive symptoms and fiber tract changes in psychotic spectrum. We assume that alterations in tracts associated with emotional or cognitive processing are related to the symptomatology of psychosis.

2. Methods & materials

2.1. Participants

Altogether eighty-eight participants were included in this study, thirty-two of them were patients with *euthymic BD type I* disorder (15 female, 17 male; M_{age}=39.23 [SD=12.36] years), twenty-six of them were patients with paranoid schizophrenia (13 female, 13 male; M_{age}=40.46 [9.01] years) according to DSM-IV criteria (APA, 1994), while thirty of them were healthy controls (16 female, 14 male; M_{age}=39.22 [10.36] years) (see Table 1).

All patients were recruited from the Department of Psychiatry, Goethe-University, Frankfurt, Germany. They had no co-occurring DSM-IV axis I or II disorders. However, BD patients have suffered from at least two major mood episodes (either depressive or manic) in their lifetime (number of depressive episodes: M=9.83 [9.65]; number of mania episodes: M=8.34 [10.03]), and SZ patients had the duration of disease at a minimum of 3 years. The mean age (M_{age}) of onset of bipolar disorder in this sample was 32.90 (10.95), and 24.31 (4.88) years for SZ patients. All patients have been taking medications at the time of enrollment, in average for 8.256 (7.14) years in BD and 7.01 (2.45) years in SZ patients. None of them received benzodiazepine drugs for at least a month prior to imaging procedures (vide infra).

Overall, BD patients' medications were categorized as: *lithium* (lithium in monotherapy or lithium + other mood stabilizers or antipsychotics), *other mood stabilizers* (other mood stabilizers in monotherapy or other mood stabilizers + other mood stabilizers or antipsychotics) and *antipsychotics* (antipsychotics in monotherapy or antipsychotics + other antipsychotics or mood stabilizers). Medications for SZ patients were categorized as: *antipsychotics in monotherapy* and *antipsychotics in dual therapy* (see Table 2 for further details on the patients' clinical characteristics). To compare different substances and doses, chlorpromazine equivalents concerning antipsychotics (see the formula by (Woods, 2003)), amitryptiline equivalents concerning antidepressant drugs (Ali, 1998), and mg of valproic acid were computed. Furthermore, a 'medication load' based on a method first introduced by Almeida (Almeida et al., 2009) was calculated. The medication load indicates mainly the amount of medication dosage (the higher the more the amount of medication), independently of the ingredients.

Control subjects did not present neurological illness or current or lifetime mental disorder (according to DSM-IV (APA, 1994)). Both groups did not differ in gender (χ^2=1.786, p=0.176), age (t=0.156, p=0.998) or years of education (t=2.821, p=0.095), and all participants were right-handed.

The procedures of the current study have been explained to all participants who thereafter provided written informed consent. The protocol of the present investigation was approved by the ethical board of the medical faculty of the Goethe-University, Frankfurt/Main, Germany.