TITLE: 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.

Running title: Deterministic fiber tracking in bipolar disorder

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Number of words in the abstract: 232 **Number of words in the text body:** 3568

Number of figures / tables: 2 / 4

Key words: structural imaging, bipolar, psychosis, fiber tracking, deterministic tractography, cognition

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 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., 2002b) 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., 200) 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; Hartberg et al., 2011; Knöchel et al., submitted; Knochel et al., 2014; Oertel-Knöchel et al., 2012; Oertel-Knochel et al., 2014; Poletti et al., 2015b)(Bauer 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; Sussman 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

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).

----------Insert Table 1 about here----------

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}) *o*f 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.

----------Insert Table 2 about here----------

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.

Assessment of psychopathology and cognitive performance

In order to assess the psychiatric history of the patient samples and of the control group as well as to rule out (comorbid) axis I and axis II mental disorders, the Structured Clinical Interview for the DSM-IV (SCID-I and SCIDII; German version: (Wittchen et al., 1996) was conducted. The Beck Depression Inventory II (BDI II; (Hautzinger et al., 2006)) was used to appraise depressive symptoms in BD patients and controls. In addition, the German version of the Bech Rafaelsen Mania Scale was administered (BRMAS; (Bech, 1981) to measure manic symptoms in BD patients and controls. Participants with SZ

completed the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987)) indicating acute symptoms of the disease. (Mass et al., 2000).

All participants completed the Mehrfachwahl-Wortschatz-Test, the German equivalent to the "Spot-the-Word test" (MWT-B; (Lehrl, 2005)) as a measure of crystallized intelligence and the Trail-making-Test as an instrument assessing psychomotor speed (TMT A) and executive functioning (TMT B) (Reitan et al., 1988). Clinical and cognitive tests are described in more detail in a previous paper that included this sample (Oertel-Knochel et al., 2014).

Assessment of WM microstructural data

Within one week after data assessment, each participant underwent three Diffusion MRI sequences using a Trio 3-T Scanner (Siemens, Erlangen, Germany) with a standard transmit-receive head coil. Diffusion MRI data was acquired with an echo planar imaging (EPI) sequence with generalized auto-calibrating parallel acquisitions (GRAPPA; (Griswold et al., 2002)) (TR = 8760 ms; TE = 100 ms; bandwith = 1302 Hz/pixel, acquisition voxel size = 2 x 2 x 2 mm^3; 60 axial adjacent slices; slice thickness = 2 mm (no gap); FOV = 192 mm x 192 mm x 120 mm; acquisition matrix = 96 x 96; averages of 10 images without (b0) and 60 images with diffusion weighting (b1000 = 1000 s/mm^2 60 noncolinear directions) (acquisition time per scan = 10 min 31 sec).

Participants were instructed to lie still and look at a white fixation cross positioned in the centre of the visual field. Moreover, they were given protective earplugs to reduce scanner noise and were asked not to engage in any overt speech throughout the scanning sequences. The data of the three DTI sequences were averaged during further preprocessing.

Tractography

All subjects were investigated through deterministic tractography using TrackVis version 0.5.2 and Diffusion Toolkit 0.6.2 (http://trackvis.org/). We chose the following four tracts: the corpus callosum (CC), the anterior thalamic radiation (ATR), the fornix (F) and the cingulum (C). The selection of these tracts has been driven by two different sources of evidence: (a) an intensive literature search, which identified potential tracts relevant for affective disorders as well as for emotional processing (view for instance the results (Emsell et al., 2013)); (b) the TBSS results of this sample published elsewhere (Oertel-Knochel et al., 2014){Knochel, 2012}. All tracts were delineated twice by two independent raters (P.O. and L.A.C), which were blind for the clinical diagnosis. In order to ensure an accurate rating, both tract delineation steps and ROI definition have been guided by a reference tractography Atlas (Stieltjes et al., 2013). Inter-rater reliability was assessed with the intraclass correlation coefficient, and it was considered high (0.91). Following a previous publication of Torgerson and colleagues (Torgerson, 2013), we computed values for the so-called indices of WM microstructural integrity: the fractional anisotropy (FA), number of fiber tracts (NofT) and tract length (Le) for left and right hemispheres. We additionally included the number of tract volumes (vol), which has been also acknowledged by previous studies as a metric of accuracy for WM integrity, in our analysis (Brandstack et al., 2013).

Delineation of tracts

We also based our technique on the study of Torgenson and colleagues (Torgerson, 2013). All tract delineations were followed by the general procedures: voxels were individually highlighted to view each appropriate tract, and then all voxels whose associated fibers were not consistent with the color of the tract of interest were

eliminated. A sphere was then positioned to assign all fibers passing through the region of interest (ROI). Secondary, all spurious fibers that passed through the sphere but did not belong to the tract of interest were removed.

Fornix (F)

Two spheres were placed to identify fibers crossing the anatomical location of the fornix. Additionally, two rectangular ROIs were drawn to remove inconsistent fibers: the first one vertically, splitting the right and left hemispheres; the other sphere was positioned to eliminate fibers belonging to the corpus callosum and anterior commissure.

Cingulum (C)

The first ROI was placed above the corpus callosum in the region characteristically identified as the cingulum. The second ROI is a rectangle drawn by free hand in the sagittal plane, splitting the right and left hemispheres. Finally, a third ROI was drawn to remove the influence of rectangular structures that commonly interfere with the delineation of the cingulate gyrus, like the corpus callosum fibers.

Anterior Thalamic Radiation (ATR)

The forelimb of the internal capsule was identified and a sphere was positioned in this ROI to cover the fibers of the ATR, with a second ROI plane drawn in the sagittal plane to remove inconsistent fibers.

Corpus Callosum (CC)

A ROI was first positioned in the sagittal plane, encompassing all fibers passing transversely in the x plan, forming the characteristic drawing of the corpus callosum; a

second ROI was positioned in the brainstem, spanning the descendant fibers of cortico spinal, bulbar tenement tracts, as well as stem fibers and the cerebellum (cerebellar peduncle medium).

Statistical analyses

All data were normally distributed and homoscedastic. We computed linear regression analyses (hierarchical), including fiber tracking scores as dependent variables and group as independent variables on a first level, and age, TMT A and TMT B as independent variables on a second level. Afterwards, post-hoc contrasts across groups were completed across groups (SZ vs. BD, BD vs. CON, SZ vs. CON). Post-hoc contrasts were only done if there was a significant effect at first level (significant group effect). Single post-hoc contrasts between groups (BD / SZ patients, BD patients / controls, SZ patients / controls). A α-level of 0.05, corrected for multiple comparisons using the Bonferroni correction, was defined as the statistical threshold. All analyses were conducted with SPSS 22.0 software package.

Bivariate correlation analyses using Pearson Product Moment correlation or Spearman Rank correlation coefficients were conducted to examine relationships between fiber tracking values and other variables of interest in each group independently (i.e. clinical scores, cognitive scores). However, only fiber tracking scores that revealed significant group effect (corrected for multiple comparisons) during comparisons were included in these analysis.

We also investigated the potential influence of medication regimens through bivariate correlation analyses (Spearman product-moment correlation, two-tailed) between fiber tracking values and medication doses, medication equivalents as well as

the duration of medication in the patient groups separately for each group of drug (antipsychotics, lithium, valproic acid).

3. Results

3.1 Cognitive and Clinical data

Significant group differences across groups were observed for psychomotor speed (TMT A) and executive functioning (TMT B) (TMT A: F=4.983, p=0.009; TMT B: F=62.85, p<0.001; view Table 1).

BD patients had significantly higher BDI II scores when compared to control group (t = 18.85, $p \leq 0.01$). However, BRMAS scores revealed no significant group differences between BD patients and controls ($p \geq 0.05$). None of the patients or controls reached a score of > 19 in the BDI II or a score of > 7 in the BRMAS, which would indicate clinically relevant depressive symptomatology.

3.2 Fiber tracking scores

Fornix (F)

All left and right fornix indices (FA, Le, Vol, NofT) revealed a significant group effect during regression analysis (all found a p<0.05 level; see Table 3). Post-hoc single contrasts revealed significant differences between SZ patients and controls in all fornix indices without the left fornix FA. Regarding group contrast between BD patients and controls, we observed significant effects in the left and right fornix indices FA and Le. However, group contrast between SZ and BD patients revealed significant in bilateral Vol and NofT fornix indices (all p's<0.05; see Table 3, Figure 2).

----------Insert Table 3 about here ----------

On the second level of the regression analysis, we observed a significant effect of TMT A on the left and right fornix FA, and significant effect of TMT B on the left and right fornix FA as well as in the left and right fornix Le. Accordingly, age showed a significant effect on the left and right fornix Le values (all p's<0.05; see Table 3, Figure 2).

----------Insert Figure 2 about here ----------

Cingulum (C)

With regard to this bundle, significant influence of the factor group during regression analysis were exhibited for the cingulum Vol (bilaterally) and NofT (left hemisphere). We observed significant single group contrasts between SZ patients and controls and SZ patients and BD patients in the left and right cingulum Vol. Left cingulum NofT showed significant group contrasts between BD patients and controls (all p's<0.05; see Table 3, Figure 2). None of the variables of the second level regression analysis (TMT A, TMT B, age) revealed any significant influence on the cingulum fiber bundles (all p's > 0.05).

Anterior thalamic radiation (ATR)

A significant group effect was also displayed for the left ATR Vol and Le and the right ATR Vol and Le (all p's<0.05; see Table 3). This effect was driven by significant group contrasts between SZ patients and controls and SZ and BD patients in these indices (all p's<0.05; see Table 3, Figure 2). As well, none of the variables of the second level regression analysis (TMT A, TMT B, age) revealed any significant influence on the ATR fiber bundles (all p's > 0.05).

Corpus Callosum (CC)

In the corpus callosum, Le and NofT indices showed a significant group effect. Such findings could be noted, for both variables, by significant contrasts between SZ patients and controls and SZ and BD patients, and also by significant contrasts between BD patients and controls in CC Le (all p's<0.01; see Table 3). Again, none of the variables of the second level regression analysis (TMT A, TMT B, age) revealed any significant influence on the corpus callosum fiber bundles (all p's > 0.05).

3.3 Secondary regression analysis

A second regression model, including fornix values as dependent variables and diagnostic groups (BD patients, SZ patients), age, age at onset and TMT B as independent variables was computed, in order to examine whether the observed alterations in fornix were influenced by age or age at onset. However, this regression analysis did not reveal any significant improvement in explaining variances (p>0.05). Therefore, we did not report the results in detail here.

3.4 Correlation analyses

Fiber tracking scores and cognitive and clinical data

There were several significant associations between psychomotor speed (TMT A) and executive functioning (TMT B) and left and right fornix Le and FA across groups.

However, the significant correlations between cognitive variables and fornix fiber tracking scores were mainly driven by the SZ group: in this subsample, psychomotor speed was inversely correlated with left and right fornix FA, and executive functioning was negatively associated with left and right fornix Le and FA. Age was also negatively correlated with right fornix Le in this sample. Regarding the BD patient group, both age and age at disease onset were significantly negative associated with right fornix Le. In

controls, executive functioning (TMT B) scores correlated significantly with left and right fornix Le, and age was significantly associated with left fornix Le and right fornix Le.

----------Insert Table 4 about here----------

Control for medication influence

We observed no significant correlation between fiber tracking scores and medication load, equivalents scores for antipsychotics, lithium, valproic acid or time of exposure to medication (all *p*'s>0.05).

4. Discussion

In this study, DTI deterministic tractography has been carried out to investigate WM microstructure abnormalities in pre-defined fiber tracts of SZ and BD subjects compared to controls; in addition, WM abnormalities were measured in association with clinical and cognitive symptomatology. We showed three main findings that deserve in-depth discussion.

First, our study showed widespread alterations in fiber tracking scores in SZ patients compared to controls, and much less differences in BD patients compared to controls. Importantly, the differences in BD patients compared to controls were mainly located in the bilateral fornix, whereas SZ patients showed differences in all chosen tracts independently of the indices (FA, Le, Vol, NofT). These results confirm the assumption that SZ patients have more severe WM changes than BD patients (Ellison-Wright and Bullmore, 2010; Friedman et al., 1999; Ivleva et al., 2012; Janssen et al., 2008; McIntosh et al., 2004; Yu et al., 2010). Contrasting with the relatively limited evidence on tractography in BD, volumetric studies have reported a number of morphometric changes

in predominantly frontal, temporal, fronto-temporal, fronto-thalamic and limbic WM regions in euthymic and / or symptomatic BD samples (Arnone et al., 2008; Delaloye et al., 2011; Ellison-Wright and Bullmore, 2010; Emsell et al., 2014; Hulshoff et al., 2012; McDonald et al., 2005; McIntosh et al., 2005; McIntosh et al., 2006; Selvaraj et al., 2012). Conversely, several studies also reported no volumetric changes in remitted bipolar patients (e.g. (Houenou et al., 2007; Zanetti et al., 2009)). These heterogeneous findings regarding WM integrity, density or volumes in BD likely results from the inclusion of participants in different illness states (i.e., remitted, acute depressive, acute manic), clinical heterogeneity (Houenou et al., 2015) as well as the use of different analytic techniques to identify morphological changes across studies.

However, as Kumar and colleagues suggested, both disorders share some abnormalities in fiber tracts that may partly explain the functional outcome (Kumar et al., 2015). Beside bilateral fornix microstructure, SZ and BD share abnormalities in the corpus callosum Le and the left cingulum NofT. This confirms to the suggestion by Kumar and colleagues who identified five clusters (callosal, posterior thalamic/optic, paralimbic, fronto-occipital) with reduced FA in both disorders. They also recognized that a single WM integrity factor that predicted social and occupational functioning scores in patients was irrespective of the diagnostic categorization (SZ vs. BD) (Kumar et al., 2015). In sum, our results with deterministic tractography support the relevance of chosen fiber tracts, as those may be crucial for a set of cognitive dimensions, particularly executive and psychomotor performance.

Secondly, as a major result, we observed differences in the fiber tracking scores of the bilateral fornix in both patient groups with most meaningful results exhibited in the SZ patient group compared with BD patients and controls. These results may be considered relatively new, as this fornix has been less frequently examined in major

psychosis disorder. Regarding the functional relevance of these tracts, they are part of the limbic system and are known to be involved in memory processing (Bähr and Frotscher, 2009; Emsell et al., 2014; Ulfig, 2008), while the fronto-limbic connections play a pivotal role in emotional processing (Adler et al., 2005; Sussmann et al., 2009). Fornix WM abnormalities in SZ patients have been observed previously using voxel-based (e.g., Guo et al., 2012) and tract-based DTI analyses (e.g., (Fitzsimmons et al., 2014)). However, the fornix WM microstructure has been less frequently examined. The existing results were controversial, showing no major structural changes in this region in BD (al., 2008; Barysheva et al., 2013), but also FA changes in the fornix in BD (Barnea-Goraly et al., 2009; Oertel-Knochel et al., 2014). However, none of the aforementioned studies employed deterministic tractography. Indeed, regardless the limited evidence of tractography, the few existing studies support our findings (Emsell et al., 2013; Sarrazin et al., 2014; Toteja et al., 2014). However, technical limitations of previous DTI studies might account for the lack of evidence involving the fornix, as acknowledged by more recent investigations (Emsell et al., 2013). Despite of the limited evidence, our findings are in line with other investigations, for instance, one reporting decreased FA in the left fornix (Emsell and al, 2015). In addition, it has been suggested the compression of the fornix as one possible cause of BD (Xu et al., 2007) and fornix alterations have been associated with the early occurrence of bipolarity among adolescents (Chao et al., 2009)). Finally, our findings for the fornix highlight the importance of this bundle, particularly for the emotional and cognitive processing, namely the integration of several limbic regions, such as the septal nuclei, nucleus accumbens, thalamus, cingulate cortex, and also, as the main efferent pathway of hippocampal networks (Behrens and Jbabdi, 2009).

There were several negative correlations between psychomotor speed and executive functioning and bilateral fornix Le and FA in SZ patients and controls (only

executive functioning), but not in BD patients. Results herein reported highlight the importance of fornix, whose altered circuitry connections to the temporal lobe, prefrontal cortex and hippocampal formation (Eisenberg, 2010), among SZ individuals, may have lead to deregulation of the aforementioned cognitive functions.

Additionally, reductions in fractional anisotropy of temporal white matter, including the fornix (Fitzsimmons et al, 2009) and inferior longitudinal fasciculus (Ashtari et al, 2007), suggest compromised integrity of key bidirectional white matter tracts of the hippocampus, including those that communicate with the prefrontal cortex.

We further analysed whether the inclusion of age and age at onset improved the explained variance of our regression model, in order to examine whether the observed alterations in fornix are related to neurodegenerative (age) versus neurodevelopmental (age at onset) factors or simply reflect the relationship with executive dysfunction. In our study, we failed to find any associations with age of onset and fornix values in the patient groups. Importantly, this finding suggests that both of these cognitive domains may at least partially explain some of the differences evidenced between BD and SZ patients. Indeed, previous findings showed also correlations between structural imaging markers and cognitive test performance in SZ (e.g., (Ehrlich et al., 2011; Ehrlich et al., 2010; Hartberg et al., 2010; Hartberg et al., 2011; Oertel-Knöchel et al., 2012)). Furthermore, significant associations between decreased WM integrity and cognitive performance in BD have also been reported previously (Haller et al., 2010; Kafantaris et al., 2009; Poletti et al., 2015a). For instance, Kafantaris and colleagues (Kafantaris et al., 2009) showed that orbito-frontal WM integrity reduction was significantly correlated with slower performance in visuo-motor processing in adolescent BD. However, the number of studies investigating the association between WM abnormalities and cognitive performance in BD remain scarce in the literature.

Another worthy of note finding is that neither acute depressive (BDI II), acute manic (BRMAS) symptoms in BD nor acute psychotic symptoms in SZ were significantly correlated with any of the fiber tracking scores across groups. Nevertheless, we have to emphasize that only non-acute or remitted patients were enrolled in our study, resulting in relatively low symptom severity scores. Although there are some reports of state-dependent changes in WM integrity (e.g. (Sussmann et al., 2009; Versace et al., 2008; Zanetti et al., 2009), most studies report relatively consistent WM alterations independent of acute symptoms (Chaddock et al., 2009; Haller et al., 2011; Oertel-Knochel et al., 2014; Wessa et al., 2009; Yurgelun-Todd et al., 2007).

In general, the underlying mechanisms related to fiber integrity loss in psychosis remain ambiguous (Schneider et al., 2012). Some authors have highlighted the role of genetic risk factors (Benedetti et al., 2015; Marlinge et al., 2014), while alternative mechanisms, e.g., loss of axonal density and diameter, neuronal loss, localized water content or a reduced myelination have also been proposed (Benedetti et al., 2011b; Beyer et al., 2005; Chaddock et al., 2009; Kafantaris et al., 2009; Mahon et al., 2010; Regenold et al., 2007; Tkachev et al., 2003)). Additionally, the specificity of tractography has been criticized (Koerte and Muehlmann, 2014). One common problem acknowledged by authors refers to the interpretation of diffusion in crossing fibers zones (Behrens and Jbabdi, 2009), for instance, the cingulum fibers. It is generally assumed by DTI that all vectors within one voxel follow a single direction or, alternatively, that all diffusion vectors belong to the same WM fiber, what may ultimately overestimate water diffusion in these areas. Finally, the interpretation of tract measurements herein presented may be puzzling and lack specificity as heterogeneous results have been reported in other investigations; for instance, major tract alterations among SZ individuals include arcuate fasciculus (Wu et al., 2015), cingulum (Voineskos, 2010), striatum and thalamus(Ellison-

Wright et al., 2014). Accordingly, the meaning of such volumetric or length alterations (both increase and decreases), particularly what it is revealed in terms of disease progression, still awaits further elucidation. In despite of such constraints, it is also accepted that tractography results are more specific than Tract based Spatial Statistics (TBSS) or ROI-oriented studies (Koerte and Muehlmann, 2014).

Another widely discussed problem of studies with psychotic patients is the heterogeneity of the symptoms and the different illness episodes patients' experience. Since BD patients were assessed during depressive state (Bremner et al., 2002; Lacerda et al., 2004; Lai et al., 2000), during manic or during remitted episodes (Oertel-Knochel et al., 2014) – and equally for SZ patients in acute or non-acute state - results are likely to be influenced by those factors. Additionally, some studies investigated only BD I patients, others included BD II or schizoaffective disorder patients as well; i.e. only a few studies have controlled for potential psychotic symptoms while others have not. Therefore, considering differences in sample selection, it is difficult to compare the results of different studies directly. This may be one reason for the heterogeneity of WM microstructural findings in BD that range from decreases, no differences up to increases in various regions. However, in this study we employed very strict inclusion criteria for the patient sample in order to ensure a high level of homogeneity. Furthermore, we used a newer and improved approach to detect WM changes.

Although the influence of psychopharmacological drugs as biasing variables on morphological alterations has been discussed for SZ and BD (Dazzan et al., 2005; Hafeman et al., 2012; Moncrieff and Leo, 2010; Moore et al., 2000; Phillips et al., 2008), we did not observe a clear influence of drug exposure on our findings. For instance, Manetti et al. (2014) reported that first-line medications for BD – such as lithium or other mood stabilizers – may have a substantial influence on myelination processes and as a result on

microstructural changes in BD. Therefore, Marlinge and colleagues (Marlinge et al., 2014) suggested to evaluate potential effects of pro-myelinating drugs on WM findings in BD.

In summary, we identified micro-anatomical changes in the bilateral cingulum, bilateral fornix, corpus callosum and bilateral anterior thalamic radiation using different scores (Le, Noft, Vol, FA) in SZ, and less pronounced abnormalities in BD patients (mainly fornix, left cingulum NofT and corpus callosum Le). The functional relevance of fornix tract alterations for cognitive performance has been shown by significant association to executive functioning and psychomotor speed in SZ patients, but not in BD. While cognitive outcomes are generally milder in the latter, current evidence indicates a continuum of symptomatic, cognitive and functional outcome across these diagnoses (Johnstone et al., 1992). Conversely, although DTI findings are usually found in the spectrum of psychotic-related disorders, overt microscopic alterations may be more often noticed in SZ (Kumar et al., 2015). Moreover, current findings suggest that cognitive symptoms are closely associated with WM changes in the fornix, at a greater (and significant) extent in SZ than in BD. Finally, our results reflect the pivotal role of this anatomical structure in the fronto-limbic circuitry modulating emotional and cognitive response in psychotic related syndromes. Our findings open important avenues for further research, for instance, prospective studies exploring micro-anatomical and WM structural abnormalities in psychosis, as the significance of these parameters in terms of disease progression and cognitive features.

Acknowledgements:

MRI was performed at the Frankfurt Brain Imaging Centre, supported by the German Research Council (DFG) and the German Ministry for Education and Research (BMBF; Brain Imaging Center Frankfurt/Main, DLR 01GO0203). We acknowledge the Brazilian National Council of Research (CNPq) for funding Dr. Gilberto S. Alves, who is supported by a post-doctoral scholarship from the CNPq (process 209981/2013-0) in an exchange cooperation program with the Goethe University, Frankfurt am Main, Germany and Dr. Andre F Carvalho, who receives CNPq research fellowship awards (level II).

Declaration of interest:

The authors report no conflict of interest.

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 = Mehrfachwahl-Wortschatz-Test

TMT = Trail Making Test

EPI = echo planar imaging

ATR = anterior thalamic radiation

F = Fornix

C = Cingulum

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Tables:

Table 1: Socio demographic and clinical characteristics of the SZ patient group (SZ Patients; n = 26), the BD patient group (BD Patients; n=32) and the control group (CON; n=30). Abbreviations: SZ = Schizophrenia, BD = Bipolar, MWT-B= Multiple Choice Word Comprehension Test, TMT = Trail making Test, BDI II=Beck-Depression scale, BRMAS = Bech-Rafaelsen-Mania Scale, PANSS=Positive and Negative Syndrome Scale. Abbreviations: M = arithmetic middle; SD = standard deviation. * = significant at a p<0.05 level, ** = significant at a p<0.01 level.

	SZ Patients	**BD Patients**	**Controls**	**Significance**
Sample Size	26	32	30	-
Gender	13 female, 13 male	15 female 17 male	16 female 14 male	χ^2=1.78, *p*=0.17
Age **Years** (*M, SD*)	40.46 (9.01)	39.23 (12.367)	39.22 (10.36)	*F*=0.12, *p*=0.88
Years of education (*M, SD*)	15.07 (2.22)	15.36 (2.34)	16.25 (1.77)	*F*=2.48, *p*=0.09
TMT A (*M, SD*)	36.31 (2.674) SZ/CON: *p*=0.03* SZ/BD: ns	36.83 (12.79) BD/CON: *p*=0.018*	27.06 (7.84)	*F*=4.983, *p*=0.009**
TMT B (*M, SD*)	146.69 (40.74) SZ/CON: *p*<0.001** BD/SZ: *p*<0.001**	79.16 (33.609) BD/CON: *p*=0.015*	56.31 (17.16)	*F*=62.85, *p*=<0.001**
MWT-B *(M, SD)*	30.84 (0.522)	31.53 (2.57)	30.17 (3.22)	*F*=2.038, *p*=0.137
BDI II (*M, SD*)	-	10.40 (9.57)	2.28 (4.36)	*t* = 18.85, *p* < 0.01**
BRMAS (*M, SD*)	-	0.767 (1.887)	0.59 (1.07)	*t* = 0.200, *p* = 0.657
PANSS (*M, SD*)	67.00 (13.65)	-	-	-

936 **Table 2:** Clinical characteristics and psychiatric medication in the SZ patient group
937 (n=26) and in the BD patient group (n = 32). SZ = Schizophrenia, BD = Bipolar, M =
938 arithmetic middle; SD = standard deviation.

Variables	BD patients	SZ patients
Number of depressive episodes *M (SD)*	9.83 (9.65)	-
Number of manic episodes *M (SD)*	8.34 (10.03)	-
Age of onset *(M* years *[SD])*	32.90 (10.95)	24.30 (4.88)
Years of taking medication *(M* years *[SD])*	8.25 (7.14)	7.01 (2.45)
Medication category	**lithium** (n = 7) lithium + antidepressant (n = 2) lithium + other mood stabilizers (n = 4) lithium + antipsychotics (n = 3) *Sum: n = 16*	**antipsychotics** monotherapy (n = 18) antipsychotics dualtherapy (n = 8)
	other mood stabilizers (n=3) other mood stabilizers + antidepressant (n = 5) other mood stabilizers + antipsychotics (n = 2) *Sum: n = 10*	**Monotherapy**: Risperidon (n = 10) Clozapin (n = 4) Quetiapin (n = 3) Olanzapin (n = 1)
	atypical antipsychotics (n = 4) antipsychotics + antidepressant (n = 2) *Sum: n = 6*	**Dual therapy**: Risperidon + Aripiprazol (n = 3) Risperidon + Flupentixol (n = 3) Olanzapin + Aripiprazol (n = 2)
Medication and medication equivalents	Chlorpromazine equivalents (mg / day): 339.85 (288.50)	Chlorpromazine equivalents (mg / day): 694.75 (929.33)
	Amitriptyline-equivalent (mg/day): 115.23 (75.23)	
	Valproic acid (mg/ day): 1204.67 (834.65)	
	Medication load (Almeida): 2.96 (1.35)	

939

Table 3: Results of the regression analysis (linear, hierarchical), including fiber tracking scores as dependent variables and group as independent variables on a first level, and age, TMT A and TMT B as independent variables on a second level. Afterwards, post-hoc contrasts across groups were done (SZ vs. BD, BD vs. CON, SZ vs. CON). We only report second level results and post-hoc contrasts if there was a significant effect at first level (significant group effect). Abbreviations: SZ = Schizophrenia, BD = Bipolar, CON = controls, *M* = arithmetic mean; n = sample size; *SD* = standard deviation; F = fornix, C = cingulum, ATR = anterior thalamic radiation, CC = corpus callosum, FA = fractional anisotropy, Vol = volumes, Le = tract length, NofT = number of tracts, l = left, r = right. * = significant at a p<0.05 level, ** = significant at a p<0.01 level, ns=not significant.

Tract	**SZ Patients** ***M (SD)*** Post-hoc *t[df=54]*	**BD Patients** ***M (SD)*** Post-hoc t[df=56]	**Controls** ***M (SD)*** *Post-hoc t[df=60]*	**Regression** ***B(SD), β, p***
l. fornix FA	0.324 (0.026) SZ vs. CON: ns	0.323 (0.049) SZ vs. BD: ns	0.343 (0.025) BD vs. CON: *p*=0.04*	Group: *B*=-0.02(0.01), *β*=-0.27, *p*=0.04* TMT A: *B*=0.001(0.001), *β*=0.419, *p*=0.01* TMT B:*B*=-0.001 (0.001), *β*=-0.394, *p*=0.02*
r. fornix FA	0.310 (0.025) SZ vs. CON: p<0.001**	0.323 (0.044) SZ vs. BD: ns	0.343 (0.021) BD vs. CON: *p*=0.04*	Group: *B*=-0.02 (0.01), *β*=-0.30, *p*=0.03* *TMT A:B=-0.02 (0.01), β=-0.29, p=0.02** *TMT B: B=-0.001 (0.002), β=-0.21, p=0.04**
l. fornix Vol	17.855 (4.251) SZ vs. CON: p<0.001**	9.654 (1.964) SZ vs. BD: p<0.001**	9.192 (2.649) BD vs. CON: ns	Group: *B*=-0.02 (0.01), *β*=-0.15, *p*=0.04*
r. fornix Vol	20.893 (4.918) SZ vs. CON: p<0.001**	10.473 (3.395) SZ vs. BD: p<0.001**	9.250 (2.791) BD vs. CON: ns	*Group: B*=0.201 (0.86), *β*=-0.243, *p*=0.04*
l. fornix Le	44.253 (11.354) SZ vs. CON: 0.011*	51.543 (17.424) SZ vs. BD: p=0.168	55.357 (12.364) BD vs. CON: *p*=0.04*	Group: *B*=-0.49 (0.17), *β*=-0.37, *p*=0.005* *TMT B: B*=-0.89 (0.09), *β*=-0.28, *p*=0.04* *Age: B*=-0.51 (0.12), *β*=-0.31, *p*=0.01*

r. fornix Le	39.206 (9.479) SZ vs. CON: *p*=0.023*	44.834 (15.020) SZ vs. BD: ns	47.484 (12.693) BD vs. CON: *p*=0.048*	*Group: B*=-0.28 (0.19), *β*=-0.30, *p*=0.03* *TMT B: B*=-0.31 (0.08), *β*=-0.41, *p*=0.01* *Age: B*=-0.63 (0.14), *β*=-0.52, *p*<0.01*
l. fornix NofT	673.00 (202.046) SZ vs. CON: *p*<0.001**	296.06 (131.180) SZ vs. BD: *p*<0.001**	336.27 (146.95) BD vs. CON: ns	Group: *B*=1.86 (1.73), *β*=0.26, *p*=0.04*
r. fornix NofT	913.73 (267.396) SZ vs. CON: *p*<0.001**	290.94 (170.584) SZ vs. BD: *p*<0.001**	361.23 (176.062) BD vs. CON: ns	Group: *B*=-0.21 (0.18), *β*=-0.32, *p*=0.04*
l. cingulum FA	0.495 (0.038)	0.487 (0.041)	0.497 (0.020)	Group: *B*=-0.01 (0.009), *β*=-0.16, *p*=0.21
r. cingulum FA	0.456 (0.036)	0.460 (0.041)	0.473 (0.025)	Group: *B*=-0.007 (0.01), *β*=-0.10, *p*=0.48
l. cingulum Vol	13.912 (2.847) SZ vs. CON: *p*<0.001**	11.161 (3.160) SZ vs. BD: *p*=0.001**	10.229 (2.221) BD vs. CON: ns	Group: *B*=1.89 (0.75), *β*=0.34, *p*=0.01*
r. cingulum Vol	12.728 (3.025) SZ vs. CON: *p*=0.004**	10.742 (3.195) SZ vs. BD: *p*=0.036*	10.225 (2.421) BD vs. CON: ns	Group: *B*=-0.11 (0.04), *β*=-0.45, *p*=0.01*
l. cingulum Le	84.103 (25.072)	76.971 (17.725)	73.380 (9.288)	Group: *B*=4.87 (4.10), *β*=0.17, *p*=0.24
r. cingulum Le	71.728 (21.780)	68.492 (13.285)	68.509 (8.335)	Group: *B*=-0.12 (3.22), *β*=-0.006, *p*=0.96
l. cingulum NofT	302.88 (68.379) SZ vs. CON: ns	321.60 (82.720) SZ vs. BD: ns	275.81 (73.383) BD vs. CON: *p*=0.047*	Group: *B*=51.50 (22.42), *β*=0.32, *p*=0.02*
r. cingulum NofT	288.15 (82.087)	290.80 (112.441)	271.75 (69.162)	Group: *B*=8.30 (24.41), *β*=-0.04, *p*=0.73
l. ATR FA	0.413 (0.047)	0.423 (0.041)	0.432 (0.032)	Group: *B*=-0.05 (0.58), *β*=0.01, *p*=0.92
r. ATR FA	0.409 (0.040)	0.428 (0.039)	0.432 (0.035)	Group: *B*=-0.004 (0.01), *β*=-0.04, *p*=0.74
l. ATR Vol	7.247 (3.103) SZ vs. CON: *p*=0.011*	5.231 (1.699) SZ vs. BD: *p*=0.006*	5.779 (2.504) BD vs. CON: ns	Group: *B*=-0.01 (0.01), *β*=-0.29, *p*=0.04*

r. ATR Vol	7.813 (3.038) SZ vs. CON: *p*=0.007*	5.754 (1.805) SZ vs. BD: *p*=0.008*	5.779 (2.504) BD vs. CON: ns	Group: *B*=0.12 (0.64), *β*=0.35, *p*=0.03*
l. ATR Le	96.082 (21.730) SZ vs. CON: *p*<0.001**	62.026 (24.816) SZ vs. BD: *p*<0.001**	65.719 (26.405) BD vs CON: ns	Group: B=-7.05 (6.83), *β=-0.27, p=0.04**
r. ATR Le	92.915 (13.895) SZ vs. CON: *p*<0.001**	67.029 (25.828) SZ vs. BD: *p*<0.001**	63.933 (29.256) BD vs. CON: ns	Group: *B*=30.32 (15.58), *β*=0.28, *p*=0.04*
l. ATR NofT	76.12 (43.957)	84.20 (44.828)	73.19 (43.901)	Group: *B*=14.93 (13.09), *β*=0.17, *p*=0.25
r. ATR NofT	87.85 (52.021)	98.83 (60.335)	78.31 (46.081)	*Group: B*=4.12 (8.18), *β*=0.07, *p*=0.61
CC FA	0.526 (0.025)	0.522 (0.042)	0.533 (0.015)	Group: *B*=-0.01 (0.009), *β*=-0.23, *p*=0.10
CC Vol	158.553 (25.481)	145.737 (23.526)	154.937 (19.288)	Group: *B*=9.27 (13.47), *β*=0.13, *p*=0.49
CC Le	103.593 (12.041) SZ vs. CON: *p*<0.001**	70.942 (39.103) SZ vs. BD: *p*=0.002*	45.885 (42.843) BD vs. CON: *p*=0.019*	*Group: B=31.23 (11.93), β=0.36, p=0.01**
CC NofT	4028.92 (822.606) SZ vs. CON: *p*=0.001**	4883.77 (1013.571) SZ vs. BD: *p*=0.001**	4886.00 (610.366) BD vs. CON: ns	Group: *B*=-13.03 (6.23), *β*=-0.30, *p*=0.04*

Table 4: Significant correlations (Spearman rank correlation (rho)), Pearson Product Moment correlation (r); two-tailed) (Bonferroni corrected). Abbreviations: SZ = schizophrenia, BD = bipolar, CON = controls. Le = tract length, FA = fractional anisotropy, TMT B = Trail Making Test A, l = left, r = right.

	SZ patients (n = 26)	**BD patients** (n = 32)	**CON** (n = 30)	
l. fornix Le	**TMT B**: *r*=-0.523, *p*=0.003**		**TMT B**: *r*=-0.489, *p*=0.005** **age**: *r*=-0.544, *p*<0.001**	
r. fornix Le	**TMT B**: *r*=-0.621, *p*<0.001** **age**: *r*=-0.467, *p*=0.01*	**age**: *r* = -0.561, *p* = 0.001** **age of onset**: *rho* = -0.428, *p* = 0.018*	**TMT B**: *r*=-0.580, *p*=0.001** **age**: *r*=-0.568, *p*=0.001**	
l. fornix FA	**TMT A:** *r*=-0.586, *p*=0.004** **TMT B:** *r*=-0.594, *p*=0.003**			
r. fornix FA	**TMT A:** *r* =-0.462, *p*=0.01* **TMT B**: *r*=-0.592, *p*=0.003**			

Figure legend:

Figure 1: Delineation of the fiber tracts: from the global WM tracts (a), the fornix (b), cingulum (c) and the corpus callosum (d) fibers are delineated. The spheres (e) depicted in orange and red remove all voxels that pass through the ROI but do not belong to the tract of interest.

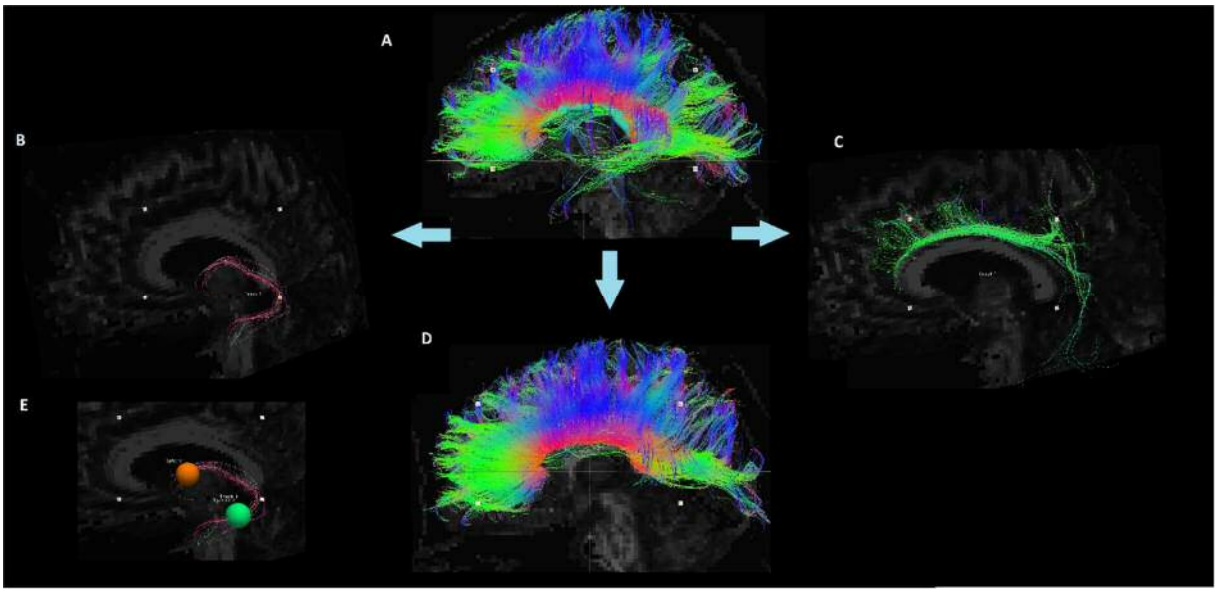
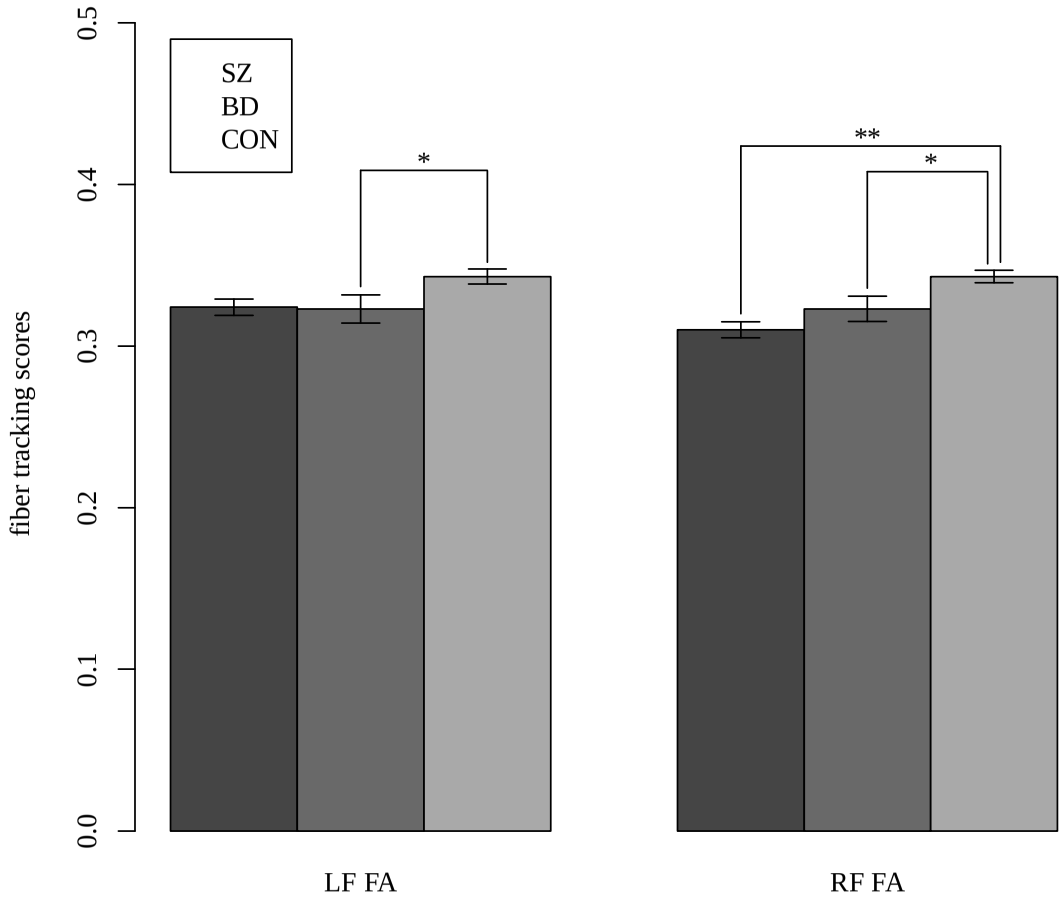


Figure 2: Group comparison of fiber tracking scores between SZ patients, BD patients and healthy controls. The figures show all comparisons which deemed significant during group contrast between SZ patients / controls, and BD patients / controls ($p<0.05$). Abbreviations: BD = BD patients, CON = controls, FA = fiber integrity, Le=length of tract, Vol = volumes, Noft = number of tracts, l = left, r = right.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CON
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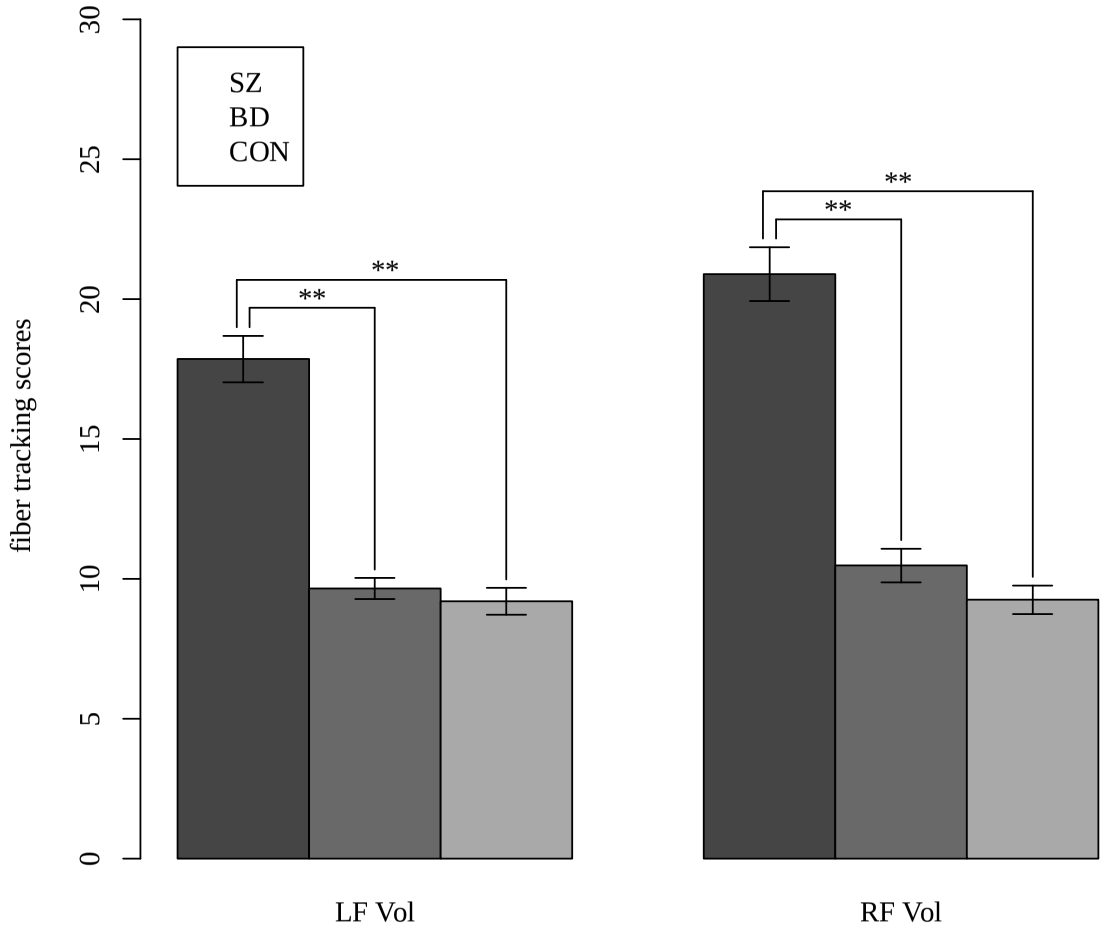
0.2
0.3
0.4
0.5
*
**
*
LF FA
RF FA

975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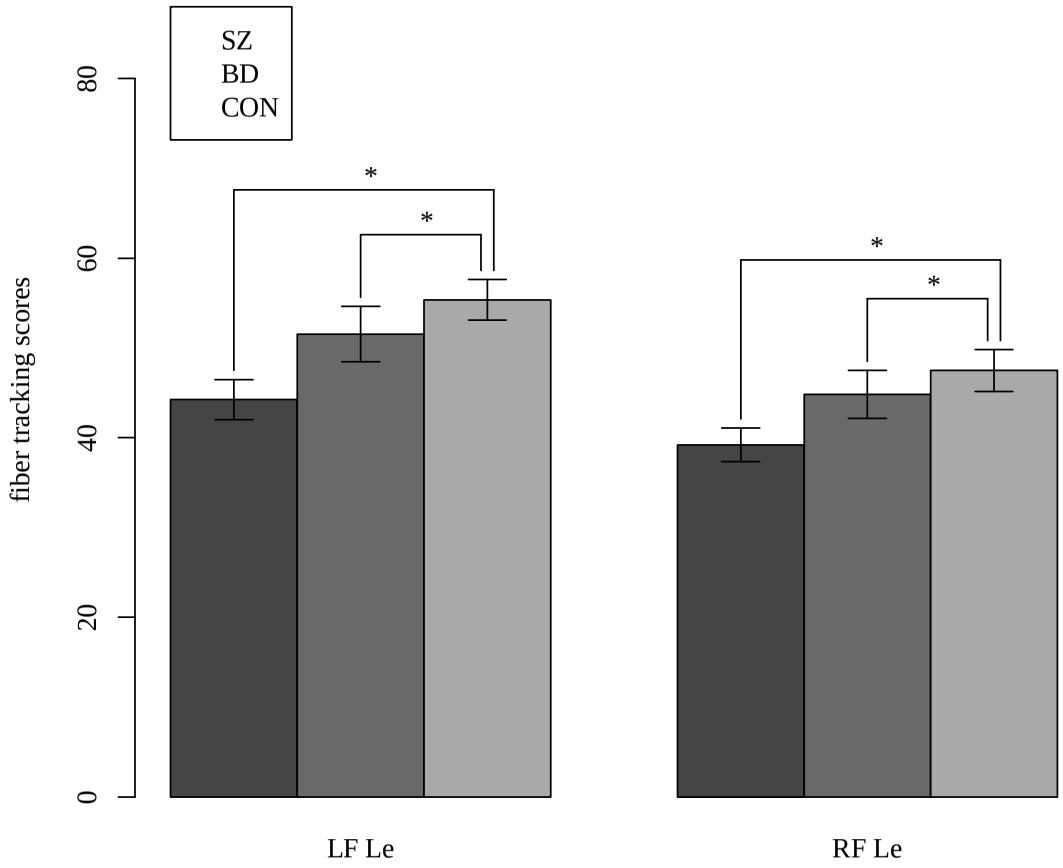
LF Vol
RF Vol

976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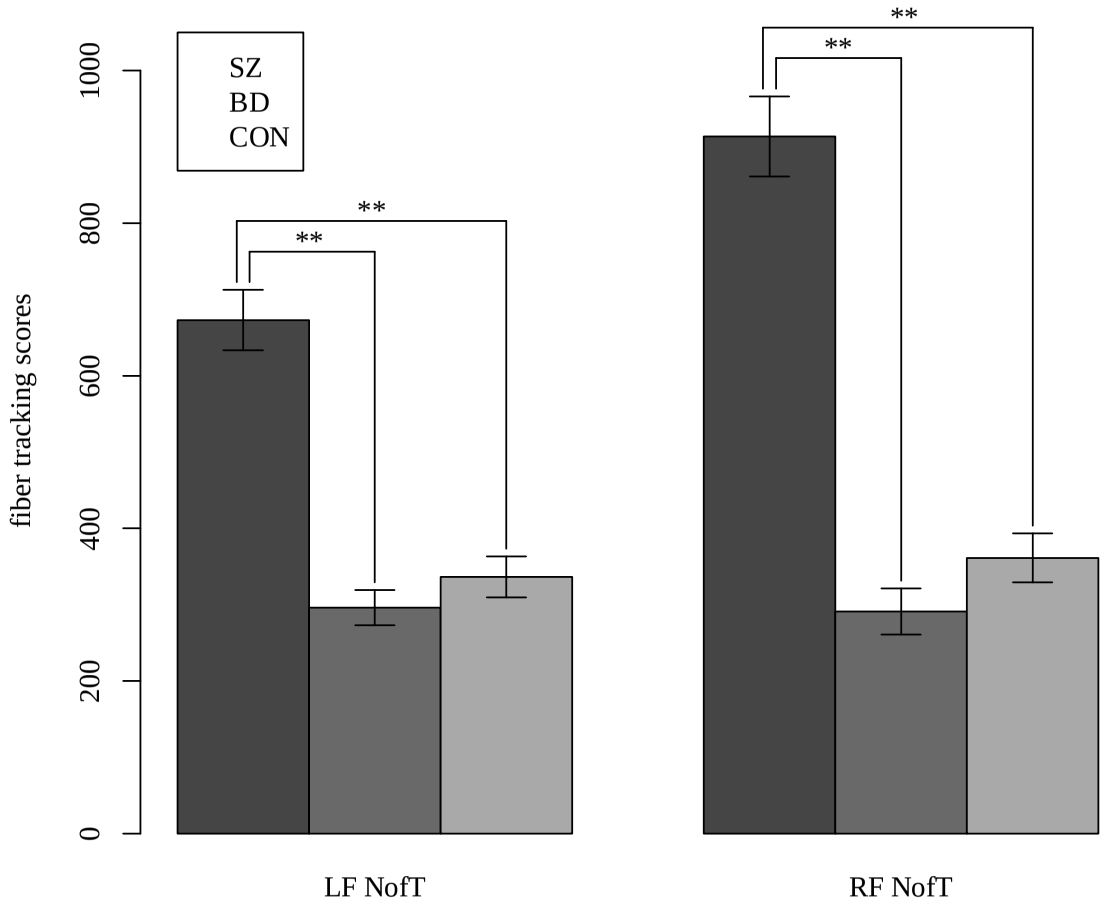
977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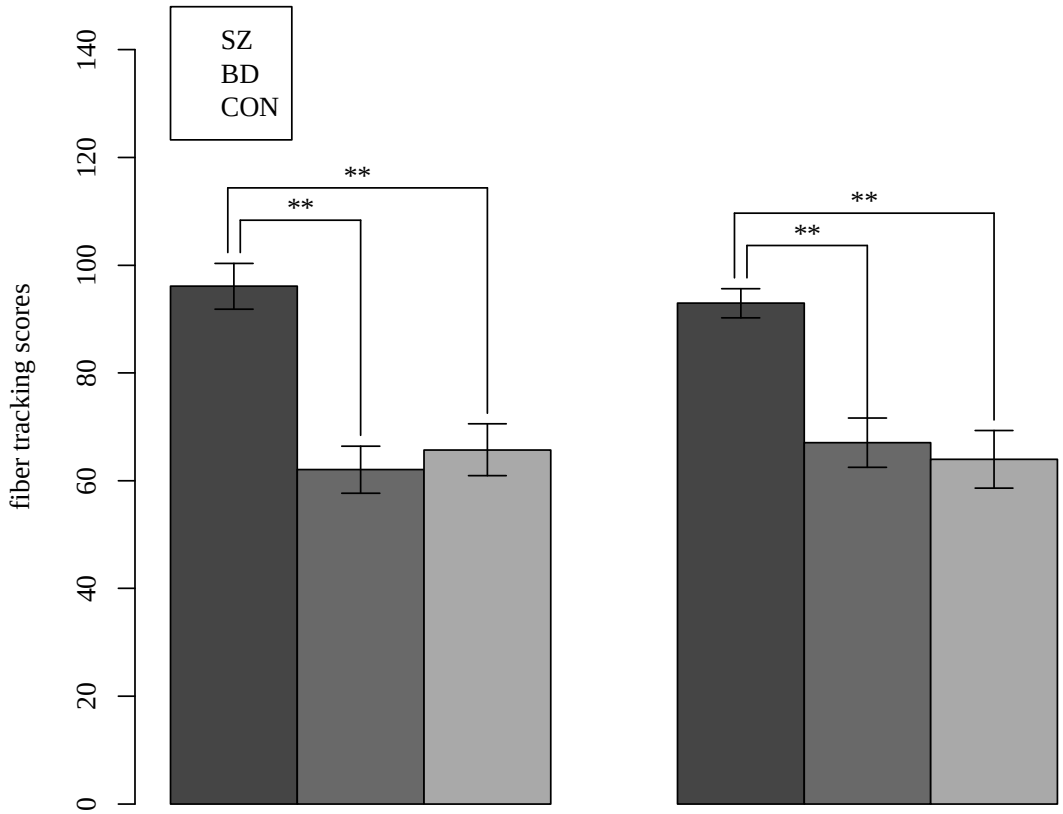
978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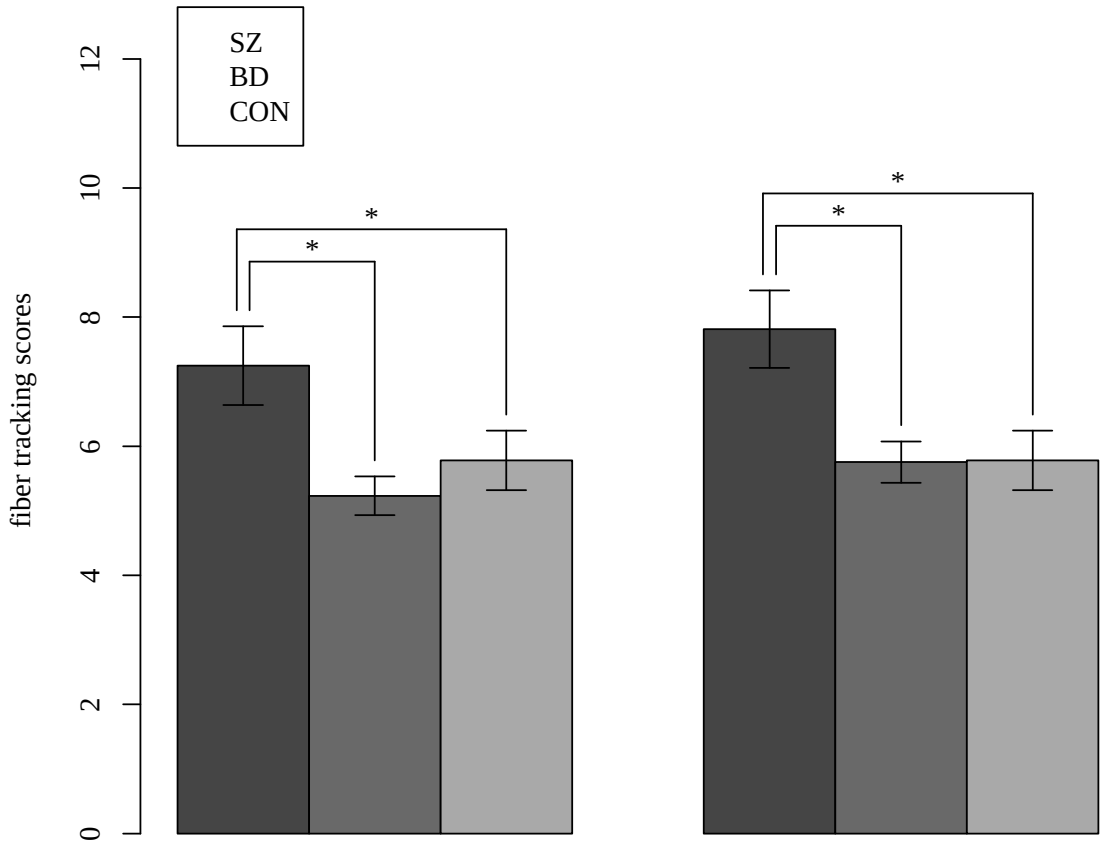
l. ATR Le
r. ATR Le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12
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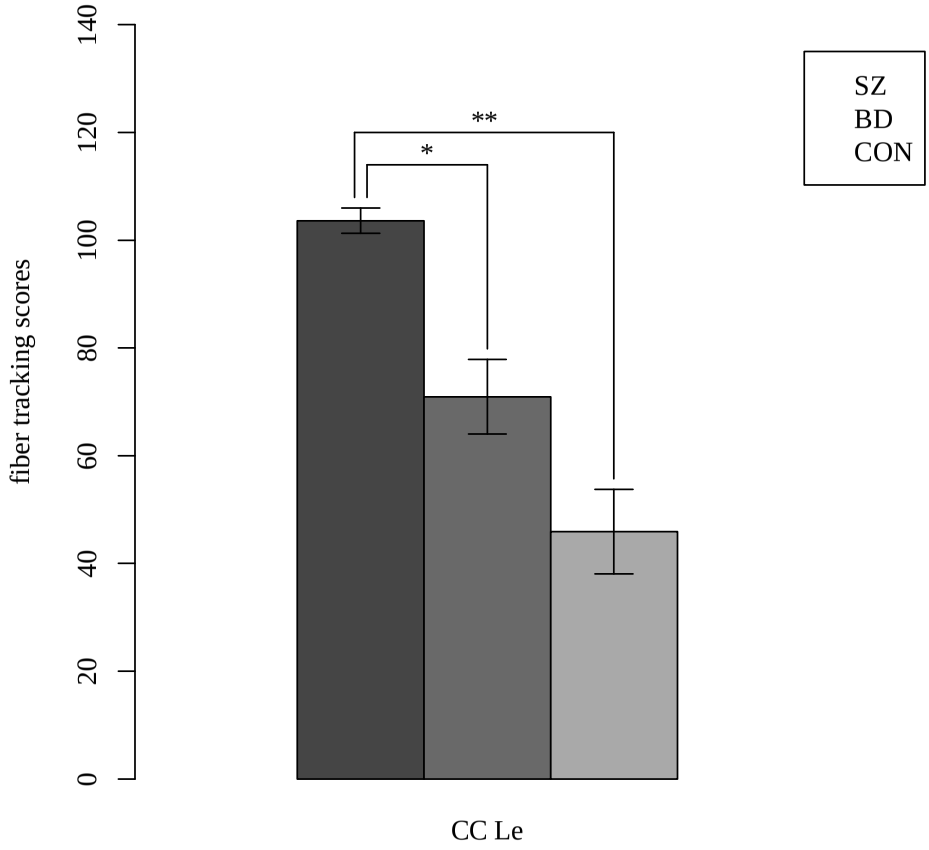
l. ATR Vol
r. ATR Vol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140
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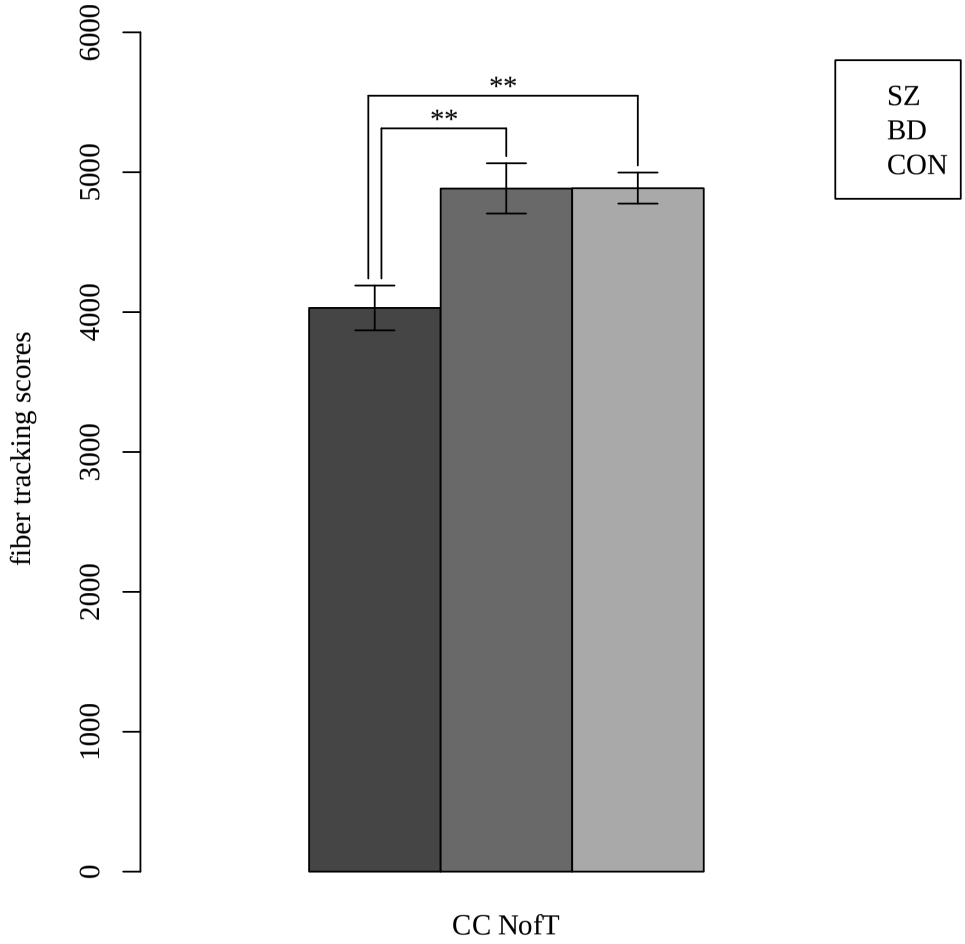
981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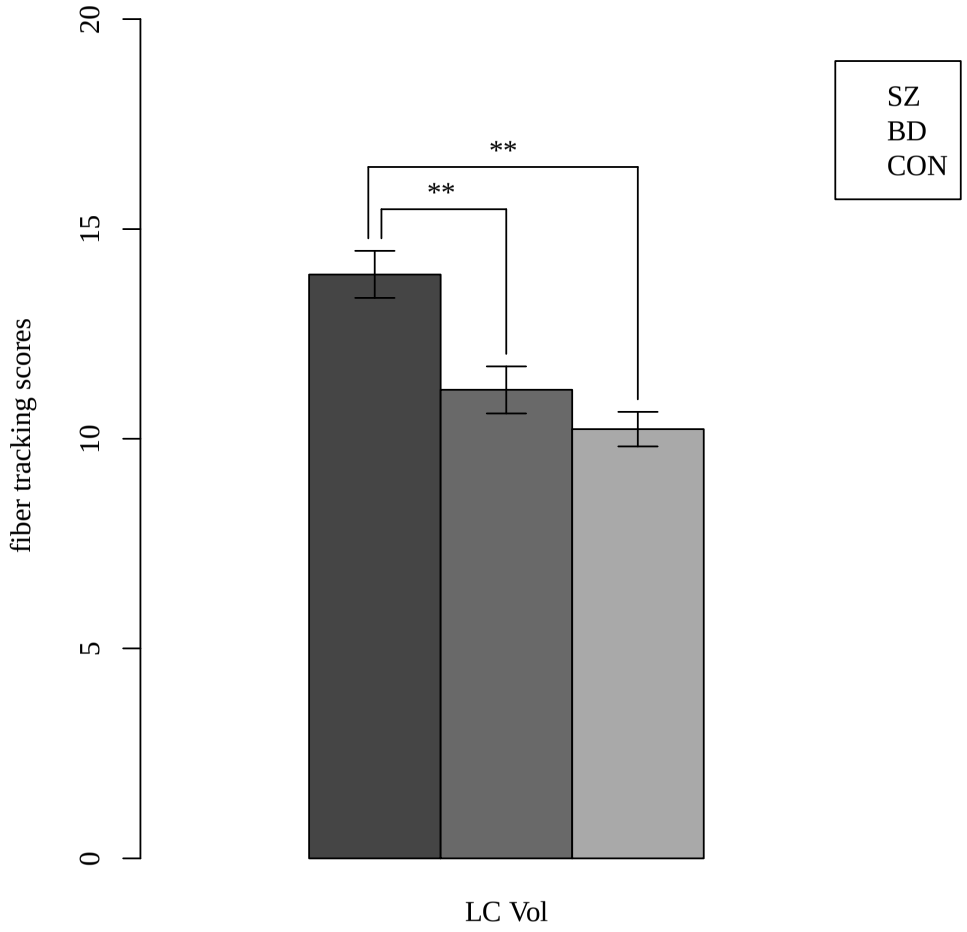
BD
CON
CC NofT

982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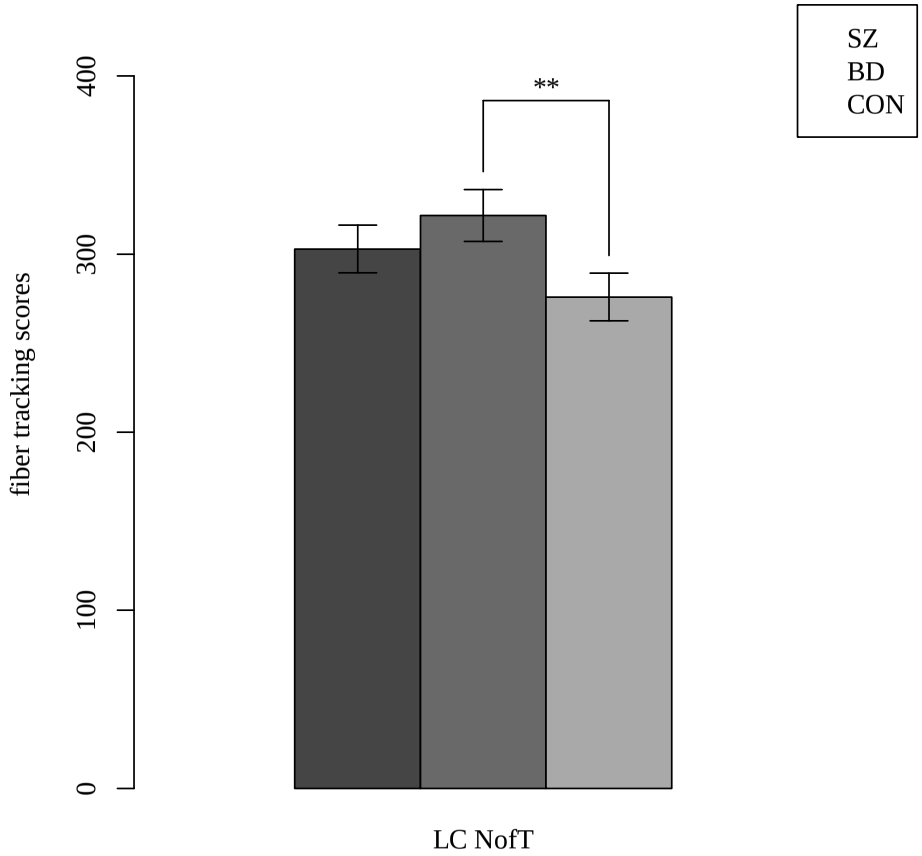
983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BD
CON
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984