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Diffusion tensor imaging of cingulum bundle and corpus callosum in schizophrenia vs. bipolar disorder

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ABSTRACT

Both schizophrenia and bipolar disorder show abnormalities of white matter, as seen in diffusion tensor imaging (DTI) analyses of major brain fibre bundles. While studies in each of the two conditions have indicated possible overlap in anatomical location, there are few direct comparisons between the disorders. Also, it is unclear whether phenotypically similar subgroups (e.g. patients with bipolar disorder and psychotic features) might share white matter pathologies or be rather similar. Using region-of-interest (ROI) analysis of white matter with diffusion tensor imaging (DTI) at 3 T, we analysed fractional anisotropy (FA), radial diffusivity (RD), and apparent diffusion coefficient (ADC) of the corpus callosum and cingulum bundle in 33 schizophrenia patients, 17 euthymic (previously psychotic) bipolar disorder patients, and 36 healthy controls. ANOVA analysis showed significant main effects of group for RD and ADC (both elevated in schizophrenia). Across the corpus callosum ROIs, there was not group effect on FA, but for RD (elevated in schizophrenia, lower in bipolar disorder) and ADC (higher in schizophrenia, intermediate in bipolar disorder). Our findings show similarities and difference (some gradual) across regions of the two major fibre tracts implicated in these disorders, which would be consistent with a neurobiological overlap of similar clinical phenotypes.

1. Introduction

Schizophrenia (Sz) and bipolar disorder (BP) share multiple clinical and neurobiological features (Pearlson, 2015). Recent imaging research indicates that grey matter changes in both disorders overlap in regions of the prefrontal cortex, the anterior cingulate cortex, and insula (Maggioni et al., 2016). Both disorders have also been associated with white matter pathology, as captured with diffusion tensor imaging (DTI). In schizophrenia, multiple white matter tracts have been shown to be affected, especially in frontal and frontolimbic areas, including the anterior thalamic radiation / anterior limb of the internal capsule, the cingulum bundle, corpus callosum and uncinate fasciculus (Samartzis et al., 2014). Similar overlap in findings, including the corpus callosum, has been found for relatives of patients with Sz and BP, respectively, pointing to a genetic factor for white matter pathologies (Arat et al., 2015). However, methods for analysis of DTI scans vary considerably, which necessitates replication of findings.

Identifying differences and similarities in the patterns of white matter pathology in Sz and BP is an important step in both identifying disease markers (e.g. for early diagnosis or intervention) as well as overlapping biological substrates or importance for both disorders (Dong et al., 2017; O'Donoghue et al., 2017).

In this study we sought to replicate and extend findings of white matter pathology in schizophrenia, and to compare them to a narrowly defined subgroup of bipolar I disorder patients with (previous) psychotic features, who are presumed to be phenotypically most similar. We focused on the cingulum and corpus callosum as the two most important white matter tracts. The cingulum bundle provides connections between the prefrontal cortex and limbic areas of the temporal lobe (Mori and Aggarwal, 2014), while the corpus callosum as the major interhemispheric tract has repeatedly been implicated in schizophrenia. Both tracts have been implicated in schizophrenia and bipolar disorder, with overlaps particularly in frontal regions, but potentially differential involvement of callosal interhemispheric connectivity; however, there are only few direct comparison studies, making inference on overlap and distinctions difficult (O'Donoghue

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et al., 2017). In addition, those few studies that have included both Sz and BP patients show heterogeneity in patient characteristics. While it is often assumed that Sz and BP share features of clinical phenotype, this assumption might only be valid for part of the BP spectrum. For example, patients with BP II and absence of psychotic symptoms over their life-time might actually bear more phenotypic similarity to patients with recurrent major depression (rather than schizophrenia). Hence, our restriction to BP I patients with previous psychotic features in the present study was chosen to compare two groups of patients with rather overlapping clinical phenotypes, yet representing two different diagnostic categories of the DSM.

2. Methods

2.1. Sample

We included a total of 86 subjects in this study, all of whom provided written informed consent to a study protocol approved by the ethics committee of Jena University Medical School: 33 schizophrenia (Sz) patients (11 female, 22 male; mean age: 33.6yrs, SD 9.5), 17 bipolar I disorder (BP) patients with previous psychotic symptoms (8 female, 9 male; mean age: 37.3yrs, SD 11.1), who were currently euthymic (no concurrent affective episode and minimal affective symptoms (Nenadic et al., 2015a, 2015b) and maximum ratings of 7 on each the Young Mania Rating Scale (Young et al., 1978) and the Hamilton Depression Scale (Hamilton, 1960)), and 36 healthy control subjects recruited from the community (18 female, 18 male; mean age: 34.7 y, SD10.8) without concurrent or previous psychiatric history or treatment and no first-degree relative with a psychotic disorder. Diagnoses were established by a board-certified psychiatrist (I.N.) according to DSM-IV-R criteria (post-hoc review confirmed that they also met DSM-5 criteria for the respective disorders). Patient groups were on stable antipsychotic or mood stabilising medication. We have previously used other imaging data from a mostly identical sample for analyses of grey matter differences (Nenadic et al., 2015a, 2015b). General exclusion criteria were traumatic brain injury, central neurological disorders, or uncontrolled major medical conditions (e.g. uncontrolled hypertension or diabetes).

The three groups did not differ significantly in age (ANOVA, $F_{(2,83)} = 0.859$, $p = 0.427$) or gender (Chi-square test, $p = 0.351$), nor in handedness (laterality quotient derived from the Edinburgh Handedness Inventory, EHI; ANOVA, $F_{(2,86)} = 2.161$, $p = 0.122$) or premorbid IQ estimated with the MWT-B test (ANOVA, $F_{(2,86)} = 0.985$, $p = 0.378$). Between the Sz and BP groups, there was no difference in age of onset (ANOVA, $F_{(1,50)} = 0.834$, $p = 0.366$) or duration of illness (ANOVA, $F_{(1,50)} = 0.896$, $p = 0.349$).

Clinical assessment included ratings of concurrent psychopathology by a board-certified psychiatrist (I.N.). Patients with schizophrenia scored a mean of 20.52 (SD 11.75) on the Scale for Assessment of Positive Symptoms (SAPS (Andreasen, 1984b)), a mean of 44.24 (SD 14.96) on the Scale for Assessment of Negative Symptoms (SANS (Andreasen, 1984a)). Patients with bipolar disorder scored a mean of 2.76 (SD 2.22) on the Young Mania rating scale (YMRS (Young et al., 1978)) and a mean of 2.65 (SD 2.29) on the Hamilton Depression Scale (Hamilton, 1960).

Among the Sz patients, n = 5 were off medication and the others received antipsychotic medication (n = 9 on aripiprazole 5–20 mg/d, n = 6 on quetiapine 50–600 mg/d, n = 2 on olanzapine 5–10 mg/d, n = 3 on risperidone 1–4 mg/d and long-acting risperidone in n = 3, furthermore n = 7 on clozapine 100–400 mg/d, n = 7 on amisulpride 100–400 mg/d and n = 1 on paliperidone 12 mg/d); in addition, augmentation was used in n = 2 with citalopram (20–40 mg/d), n = 1 with sertraline (100 mg/d), n = 2 with venlafaxine (75 mg/d) and lithium (900 mg/d) and n = 2 with pipamperone (40–80 mg/d).

Among the bipolar patients, n = 10 received lithium (400–900 mg/d), while n = 13 received atypical antipsychotic (n = 2 on aripiprazole 10–15 mg/d, n = 9 on quetiapine 25–600 mg/d, n = 2 on olanzapine 7.5–15 mg/d); also n = 3 took an antiepileptic (n = 1 oxcarbazepine 450 mg/d; n = 1 on valproic acid 1500 mg/d; n = 1 on pregabalin 150 mg/d).

2.2. MR Image acquisition and analysis

We acquired diffusion tensor imaging (DTI) scans using a twice-refocused-spin-echo EPI sequence (TR 6900 ms, TE 91 ms, 55 slices with a thickness of 2.5 mm each, 96×96 acquisition matrix interpolated to 128×128 resulting in an in-plane resolution of 1.25×1.25 mm^2, 82 diffusion weighted images with b-value of 1000 s/mm^2 and 5 volumes without diffusion weighting). Anatomical data were acquired using a MPRAGE sequence (TR 2300 ms, TE 3.03 ms, TI 900 ms, bandwidth 130 Hz/pixel, isotropic resolution $1 \times 1 \times 1$ mm^3). All MR data were acquired using a 3T scanner (Tim Trio, Siemens Medical, Erlangen Germany) with a 12-channel head-coil.

MR data were analysed using Freesurfer software (version 5.3.0, http://surfer.nmr.mgh.harvard.edu/) software, including the *recon-all* segmentation pipeline (version 1.379.2.73), *dt_recon* (version 1.15), and *bb_register* (version 1.49.2.3).

From the FreeSurfer regions-of-interest (ROIs), we selected four cingulum ROIs (rostral anterior, caudal anterior, isthmus, posterior) and five corpus callosum ROIs for further separate analysis. We investigated fractional anisotropy (FA) and radial diffusivity (RD) as our main parameters, and also the apparent diffusion coefficient (ADC). Hence, these parameters, which were obtained on a voxel-level in the first instance, were averaged across the ROI (as defined by the above atlas), and mean values for each ROI were then used for further statistical analysis.

2.3. Statistical analysis

For the analysis of both white matter structures (and each of the three diffusion parameters), we used ANOVAs with between-group factor *diagnosis* (Sz; BP; HC) and within-group factors *region* (four for cingulum, five for corpus callosum), and in the case of the cingulum also with a within-group factor *hemisphere* (left; right). For post-hoc comparisons, we used Scheffe's test.

3. Results

3.1. Cingulum bundle analyses

For the cingulum bundle, we found no significant effect of group on FA ($F_{(2,83)} = 2.135$; $p = 0.125$), but a significant group effect on RD ($F_{(2,83)} = 3.583$; $p = 0.032$), with post-hoc Scheffe's test indicating a trend for higher RD in Sz compared to HC (mean difference 0.0738; $p = 0.052$); ADC also differed between groups ($F_{(2,83)} = 3.674$; $p = 0.03$), with post-hoc testing confirming significantly higher ADC in Sz vs. HC (mean difference 0.0718; Scheffe's test $p = 0.03$). There was no significant cingulum by hemisphere by group interaction for either RD (Pillai-Spur; $p = 0.515$) nor for ADC (Pillai-Spur; $p = 0.474$).

Since the gender ratio was different across the patient groups (although this difference was not statistically significant), we re-computed ANOVA analyses (again using region as a repeated measures within-group factor) with gender as a covariate (to remove gender-related variance), and this showed no significant effect of group on FA ($F_{(2,82)} = 2.202$; $p = 0.117$) and no significant effect of gender on FA ($F_{(2,82)} = 0.199$; $p = 0.657$), a significant effect of group on RD ($F_{(2,82)} = 5.196$; $p = 0.008$) with a significant effect of gender on RD as well ($F_{(2,82)} = 8.753$; $p = 0.004$), and finally a significant effect of group on ADC ($F_{(2,82)} = 5.745$; $p = 0.005$) with a significant effect of gender on ADC as well ($F_{(2,82)} = 12.002$; $p = 0.001$). Hence, these findings are comparable to our initial analysis.