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Relationship between neuropsychological behavior and brain white matter in first-episode psychosis

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Abstract

We addressed the relationship between white matter architecture, represented by MRI fractional anisotropy (FA), and cognition in individuals with first-episode psychosis (FEP) by applying for a new methodology that allows whole brain parcellation of core and peripheral white matter in a biologically meaningful fashion. Regionally specific correlations were found in FEP between three specific domains of cognition (processing speed, attention/working memory, and executive functioning) and FA at the deep (cerebral peduncles, sagittal striatum, uncinate, internal/external capsule, cingulum) and peripheral white matter (adjacent to inferior temporal, angular, supramarginal, insula, occipital, rectus gyrus).

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Contributors

AVF: conceived and designed the analysis; contributed analysis tools, performed the analysis; wrote the paper

JC: collected data; contributed data

CY: contributed analysis tools

JH: contributed analysis tools

AK: edited the paper, contributed discussion

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Conflict of interest

The authors declare no conflict of interest.

Keywords

DTI; first-episode psychosis; schizophrenia; cognition; MRI

1. Introduction

Abnormalities in diffusion tensor images (DTI) have been reported in patients with psychotic disorders, such as Schizophrenia (SZ) (Cheung et al., 2008; Mitelman et al., 2007; Perez-Iglesias et al., 2010a; Price et al., 2007; Schmidt et al., 2015; Wang et al., 2011; Whitford et al., 2010). Decreases in fractional anisotropy (FA) have been described in major tracts and widespread areas (Kelly et al., 2017; Oestreich et al., 2017). These changes are observed in patients with psychosis in early disease stages (Lee et al., 2012) and non-medicated patients (Cheung et al., 2008; Lei et al., 2015). Furthermore, many studies have reported associations between the white matter microstructure and cognition in psychotic patients (Alloza et al., 2016; Karbasforoushan et al., 2015; Nazeri et al., 2013; Perez-Iglesias et al., 2010b).

Nevertheless, there were methodological limitations in studying specific white matter regions and structures. Studies focusing on tracts of interest (Alloza et al., 2016; Karbasforoushan et al., 2015; Nazeri et al., 2013; Perez-Iglesias et al., 2010b) suffer from the limitations of tract-tracing and population variability. Voxel-based hypothesis-free studies suffer from poor signal-to-noise ratio and imperfections in spatial normalization, particularly in the peripheral white matter (Karlsgodt et al., 2009; Kochunov et al., 2017; Kuswanto et al., 2012).

To address these limitations, we recently developed a novel method in automated brain segmentation and quantification for biologically meaningful regions of interest (Miller and Qiu, 2009; Mori et al., 2009; Tang et al., 2014). This method can be applied for the whole white matter, including the, usually neglected, peripheral association areas. This initial reduction in the dimensions of the (voxel-based) neuroimaging data increases the signal-to-noise ratio and the statistical power (Faria, 2017; Miller et al., 1997; Miller et al., 2013).

In this study, we examined white matter anisotropy of patients with first episode of psychosis (FEP) using this novel automated atlas-based segmentation method. Furthermore, we assessed the association of white matter anisotropy with cognitive changes.

2. Materials and Methods

2.1. Cohort

Individuals with FEP, as well as neurologically and psychologically healthy participants, were recruited by the Johns Hopkins Schizophrenia Center. Details about the recruitment, inclusion and exclusion criteria, demographics, and clinical features can be found elsewhere (Kamath, 2018; Kamath et al., 2018). In this study, we included individuals with FEP (n=82) [SZ (n=45), schizoaffective disorder (n=13), bipolar disorder with psychotic features (n=19), major depressive disorder with psychotic features (n=5)] and 93 healthy controls.

2.2 Neuropsychological Evaluation

A complete clinical and neuropsychological evaluation was performed. The cognitive scores were scaled in normally distributed standardized units, and grouped by "factor scores" into: 1) processing speed (calculated from the combined scores of the Grooved Pegboard test and the Salthouse test); 2) attention / working memory (Digit Span and Brief Attention Memory test); 3) verbal learning and memory (Hopkins Verbal Learning test); 4) visual learning and memory (Brief Visuospatial Memory test); 5) ideational fluency (Ideational Fluency assessment for Word Fluency and Acceptable Designs); and 6) executive functioning (Modified Wisconsin Card Sorting test). "Adjusted" scores were calculated after adjusting for age, gender, and race.

2.3. MRI and imaging processing

The MRI was obtained in the same day as the neuropsychological evaluation, on a Phillips 3T scanner. The diffusion tensor imaging (DTI) parameters were: axial orientation; TR/TE=2000/30 ms; 32 gradients; b factor=1000; voxel size=0.8281×0.8281×2.2 mm; 70 slices. The DTI was automatically processed in MRICloud (www.MRICloud.org), a public web-based service for multi-contrast, multi-atlas imaging segmentation and quantification (Mori et al., 2016). Each individual was represented by a vector of FA values in 96 brain regions, as defined by (Mori et al., 2008; Oishi et al., 2009; Oishi et al., 2011) (see supplemental material).

2.4. Statistical Analysis

After confirming the normal distribution of FA values with Shapiro-Wilk test and Q-Q plots, we used t-test to compare the global and regional FA between groups matched by age, gender, and race. Groups were defined as healthy controls, FEP, and two FEP subgroups: individuals with schizophrenia and schizoaffective disorders (S-FEP) and those with major depressive disorder and bipolar disorder with psychotic features (M-FEP). This was based on previous studies and two recent meta-analyses (Grossman et al., 1991; Maj et al., 1991; Pagel et al., 2013; Pini et al., 2001; Radomsky et al., 1999; Rink et al., 2016; Tsuang and Coryell, 1993) that found patients with schizoaffective disorders have illness characteristics similar to patients with schizophrenia, in comparison with patients with bipolar disorder or major depressive disorder with psychotic features (M-FEP).

Using linear models, we evaluated the relationship between white matter FA and the six cognitive factors in FEP group and subgroups, and controls. Significance was considered when the p-value corrected for multiple comparisons (FDR), as well as a permutation test (1000-folds), was lower than 0.1 (0.05 at one-tail regression). We chose a one-tail regression based on the previously reported positive correlation between FA and cognition (Kochunov et al., 2017). Correlations were declared significant only if they met the criteria above when using BOTH the non-adjusted and the age-, gender-, and race-adjusted cognitive scores.

For the significant relationships, we tested whether the partial correlation between FA and cognition remained significant after adjusting age, gender, race, and antipsychotic medication. Finally, we conducted interaction analysis to investigate the difference in slopes between groups (controls vs. FEP group and subgroups).

3. Results

3.1. Cohort

Controls and S-FEP differed in gender, reflecting the prevalence of the diseases (table 1). SFEP and M-FEP differed in gender and race, but not in antipsychotic medication dosages, converted to chlorpromazine equivalents using published reference tables (Woods, 2003). Information about education level, handiness, disease stage, and non-antipsychotic medications was not fully quantitatively available; therefore these factors were not included in our analysis, which is a limitation of this study.

3.2. Neuropsychological Evaluation

FEP patients scored lower than controls in all neurocognitive domains with the exception of executive functioning in which M-FEP patients did not score significantly different from controls. S-FEP scored lower than M-FEP in all cognitive scores, except for visual learning and memory, and processing speed (Table1).

3.3. Group differences in FA between FEP and controls

Compared with controls, FEP patients had significantly lower FA in the global white matter. In particular, the FEP group and the S-FEP subgroup showed lower FA than controls in the subsegments of the projection fibers (at the pons level, cerebral peduncle, internal capsule), main commissural fibers (corpus callosum), association pathways (anterior corona radiata and inferior occipital-frontal fasciculus); and higher FA in the caudate, a deep gray matter nucleus (Table 2). The M-FEP group showed similar trends, although some areas were not significantly different from controls (table 2).

3.4. Correlations between FA and cognition in FEP

Next, we studied the relationship between changes in white matter and cognitive manifestations. In FEP patients, the global white matter FA, measured by averaging all segmented areas, was positively correlated with the scores for specific domains of cognitive function, such as those of processing speed (p-value=0.005, non-adjusted score; p=0.009, adjusted score) and attention / working memory (p-value=0.029, non-adjusted score; p=0.028, adjusted score). These correlations were not observed in healthy controls.

The FEP group showed regionally-specific correlations between processing speed and white matter FA in the cerebral peduncles, the inferior temporal, the angular, and the supramarginal gyrus. Furthermore, the FEP group showed correlations between attention / working memory and the white matter FA in the occipital, the sagittal striatum, the uncinate fasciculus, and the external capsule / insula (Table 3).

The partial correlations between regional FA and function remained significant after inclusion of age, race, gender, and antipsychotic dosage in the models (Table 3, “P-mv”). Generally, the slopes of the linear models were significantly different in FEP and controls (Table 3, “P-gr.sl.”).

3.5. Correlations between FA and cognition in FEP subgroups

All significant correlations were stronger in the S-FEP sub-group than the whole FEP group (Table 3 and Figure 1). The S-FEP, but not the whole FEP group, displayed regional correlations between executive memory and white matter FA in the left cingullum, the rectus gyrus, the internal capsule, and the sagittal striatum (Table 3 and Figure 1).

The partial correlations between regional FA and function remained significant after inclusion of age, race, gender, and antipsychotic dosage in the models (Table 3, “P-mv”). In general, the slopes of the linear models were significantly different in S-FEP and controls (Table 3, “P-gr.sl.”).

There was no significant correlation between FA and cognition in the M-FEP group. Note, the M-FEP sample size limited the power of the correlational analysis.

4. Discussion

As in previous studies (Kuswanto et al., 2012) and a meta-analysis of patients with chronic SZ, we found widespread FA decrease in FEP, and a strong correlation between processing speed and executive / working memory in the core white matter and deep white matter tracts (Kochunov et al., 2017). The corroboration of these findings attests to the high power of our approach, as we used a sample size much smaller than the previous meta-analysis.

Unlike previous studies, this novel methodology enabled extension the analysis from the core to the peripheral white matter association areas, in a data-driven approach, and to report associations not previously described in FEP patients. We found that processing speed tests, driven by both motor coordination (speed of navigating the board) and semantic performance (reading and understanding the task), correlated with FA in motor (cerebral peduncles) and language processing areas (inferior temporal, angular, and supramarginal gyrus). Attention / working memory correlated with FA in the core white matter (sagittal striatum, external capsule / insula), the uncinate fasciculus (considered a locus of episodic memory and a zone of DTI abnormalities in patients with schizophrenia (Burns et al., 2003; Kitis et al., 2012; Kubicki et al., 2005; Marin et al., 2017; McIntosh et al., 2008; Price et al., 2008; Voineskos et al., 2010; Von Der Heide et al., 2013; Wilmsmeier et al., 2010), and the occipital area. Executive function correlated with FA in the white matter adjacent to frontal, rectus gyrus, and cingullum, which were previously identified as neural correlates of executive function by fMRI (Wilmsmeier et al., 2010).

The correlations between regional FA and cognition were stronger in S-FEP than in the whole FEP group, which highlights the importance of population stratification. While we did not observe such relationships in controls, previous studies using other methodologies, elderly populations, and diseases with higher effect size demonstrated similar function-anatomical relations (Aukema et al., 2009; Cacciaglia et al., 2018; Gu et al., 2013; Jirsaraie et al., 2018; Jung et al., 2012; Sasson et al., 2012, 2013; Tartaglia et al., 2012; Turken et al., 2008; Williams et al., 2017). Therefore, although such relations may not be FEP-specific, FEP patients (in particular S-FEP) present a large range of FA and cognition scores that

increases the power to detect anatomic-functional links, indirectly pointing to FA as a candidate functional biomarker.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Alloza C, Cox SR, Duff B, Semple SI, Bastin ME, Whalley HC, Lawrie SM, 2016 Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia. Psychiatry research. Neuroimaging 254, 26–33. [PubMed: 27308721]

Aukema EJ, Caan MW, Oudhuis N, Majoie CB, Vos FM, Reneman L, Last BF, Grootenhuis MA, Schouten-van Meeteren AY, 2009 White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. International journal of radiation oncology, biology, physics 74(3), 837–843.

Burns J, Job D, Bastin ME, Whalley H, Macgillivray T, Johnstone EC, Lawrie SM, 2003 Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. The British journal of psychiatry : the journal of mental science 182, 439–443. [PubMed: 12724248]

Cacciaglia R, Molinuevo JL, Sanchez-Benavides G, Falcon C, Gramunt N, Brugulat-Serrat A, Grau O, Gispert JD, 2018 Episodic memory and executive functions in cognitively healthy individuals display distinct neuroanatomical correlates which are differentially modulated by aging. Human brain mapping 39(11), 4565–4579. [PubMed: 29972619]

Cheung V, Cheung C, McAlonan GM, Deng Y, Wong JG, Yip L, Tai KS, Khong PL, Sham P, Chua SE, 2008 A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. Psychological medicine 38(6), 877–885. [PubMed: 17949516]

Faria AV, Liang Z, Miller MI, Mori S, 2017 Brain MRI Pattern Recognition Translated to Clinical Scenarios. Frontiers in neuroscience.

Grossman LS, Harrow M, Goldberg JF, Fichtner CG, 1991 Outcome of schizoaffective disorder at two long-term follow-ups: comparisons with outcome of schizophrenia and affective disorders. The American journal of psychiatry 148(10), 1359–1365. [PubMed: 1897617]

Gu L, Li J, Feng DF, Cheng ET, Li DC, Yang XQ, Wang BC, 2013 Detection of white matter lesions in the acute stage of diffuse axonal injury predicts long-term cognitive impairments: a clinical diffusion tensor imaging study. The journal of trauma and acute care surgery 74(1), 242–247. [PubMed: 23064612]

Jirsaraie RJ, Sheffield JM, Barch DM, 2018 Neural correlates of global and specific cognitive deficits in schizophrenia. Schizophrenia research 201, 237–242. [PubMed: 29954699]

Jung RE, Chavez RS, Flores RA, Qualls C, Sibbitt WL Jr., Roldan CA, 2012 White matter correlates of neuropsychological dysfunction in systemic lupus erythematosus. PloS one 7(1), e28373. [PubMed: 22291880]

Kamath V, Crawford J, DuBois S, Nucifora FC Jr., Nestadt G, Sawa A, Schretlen DJ, 2018 Contributions of olfactory and neuropsychological assessment to the diagnosis of first-episode schizophrenia. Neuropsychology in press.

Kamath V, Lasutschinkow P, Ishizuka K, Sawa A, 2018 Olfactory Functioning in First-Episode Psychosis. Schizophrenia bulletin 44(3), 672–680. [PubMed: 28981913]

Karbasforoushan H, Duffy B, Blackford JU, Woodward ND, 2015 Processing speed impairment in schizophrenia is mediated by white matter integrity. Psychological medicine 45(1), 109–120. [PubMed: 25066842]

Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD, 2009 White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. Biological psychiatry 66(6), 562–569. [PubMed: 19423081]

Kelly S, Jahanshad N, Zalesky A, Kochunov P, Agartz I, Alloza C, Andreassen OA, Arango C, Banaj N, Bouix S, Bousman CA, Brouwer RM, Bruggemann J, Bustillo J, Cahn W, Calhoun V, Cannon D, Carr V, Catts S, Chen J, Chen JX, Chen X, Chiapponi C, Cho KK, Ciullo V, Corvin AS, Crespo-Facorro B, Cropley V, De Rossi P, Diaz-Caneja CM, Dickie EW, Ehrlich S, Fan FM, Faskowitz J, Fatouros-Bergman H, Flyckt L, Ford JM, Fouche JP, Fukunaga M, Gill M, Glahn DC, Gollub R, Goudzwaard ED, Guo H, Gur RE, Gur RC, Gurholt TP, Hashimoto R, Hatton SN, Henskens FA, Hibar DP, Hickie IB, Hong LE, Horacek J, Howells FM, Hulshoff Pol HE, Hyde CL, Isaev D, Jablensky A, Jansen PR, Janssen J, Jonsson EG, Jung LA, Kahn RS, Kikinis Z, Liu K, Klauser P, Knochel C, Kubicki M, Lagopoulos J, Langen C, Lawrie S, Lenroot RK, Lim KO, Lopez-Jaramillo C, Lyall A, Magnotta V, Mandl RCW, Mathalon DH, McCarley RW, McCarthy-Jones S, McDonald C, McEwen S, McIntosh A, Melicher T, Mesholam-Gately RI, Michie PT, Mowry B, Mueller BA, Newell DT, O'Donnell P, Oertel-Knochel V, Oestreich L, Paciga SA, Pantelis C, Pasternak O, Pearlson G, Pellicano GR, Pereira A, Pineda Zapata J, Piras F, Potkin SG, Preda A, Rasser PE, Roalf DR, Roiz R, Roos A, Rotenberg D, Satterthwaite TD, Savadjiev P, Schall U, Scott RJ, Seal ML, Seidman LJ, Shannon Weickert C, Whelan CD, Shenton ME, Kwon JS, Spalletta G, Spaniel F, Sprooten E, Stablein M, Stein DJ, Sundram S, Tan Y, Tan S, Tang S, Temmingh HS, Westlye LT, Tonnesen S, Tordesillas-Gutierrez D, Doan NT, Vaidya J, van Haren NEM, Vargas CD, Vecchio D, Velakoulis D, Voineskos A, Voyvodic JQ, Wang Z, Wan P, Wei D, Weickert TW, Whalley H, White T, Whitford TJ, Wojcik JD, Xiang H, Xie Z, Yamamori H, Yang F, Yao N, Zhang G, Zhao J, van Erp TGM, Turner J, Thompson PM, Donohoe G, 2017 Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. Molecular psychiatry.

Kitis O, Ozalay O, Zengin EB, Haznedaroglu D, Eker MC, Yalvac D, Oguz K, Coburn K, Gonul AS, 2012 Reduced left uncinate fasciculus fractional anisotropy in deficit schizophrenia but not in non-deficit schizophrenia. Psychiatry and clinical neurosciences 66(1), 34–43. [PubMed: 22250608]

Kochunov P, Coyle TR, Rowland LM, Jahanshad N, Thompson PM, Kelly S, Du X, Sampath H, Bruce H, Chiappelli J, Ryan M, Fisseha F, Savransky A, Adhikari B, Chen S, Paciga SA, Whelan CD, Xie Z, Hyde CL, Chen X, Schubert CR, O'Donnell P, Hong LE, 2017 Association of White Matter With Core Cognitive Deficits in Patients With Schizophrenia. JAMA psychiatry 74(9), 958–966. [PubMed: 28768312]

Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE, Niznikiewicz M, Connor EE, Levitt JJ, Frumin M, Kikinis R, Jolesz FA, McCarley RW, Shenton ME, 2005 DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. NeuroImage 26(4), 1109–1118. [PubMed: 15878290]

Kuswanto CN, Teh I, Lee TS, Sim K, 2012 Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: a systematic review. Clin Psychopharmacol Neurosci 10(1), 13–24. [PubMed: 23429992]

Lee DY, Smith GN, Su W, Honer WG, Macewan GW, Lapointe JS, Vertinsky AT, Vila-Rodriguez F, Kopala LC, Lang DJ, 2012 White matter tract abnormalities in first-episode psychosis. Schizophrenia research 141(1), 29–34. [PubMed: 22863549]

Lei W, Li N, Deng W, Li M, Huang C, Ma X, Wang Q, Guo W, Li Y, Jiang L, Zhou Y, Hu X, McAlonan GM, Li T, 2015 White matter alterations in first episode treatment-naive patients with deficit schizophrenia: a combined VBM and DTI study. Scientific reports 5, 12994. [PubMed: 26257373]

Maj M, Starace F, Pirozzi R, 1991 A family study of DSM-III-R schizoaffective disorder, depressive type, compared with schizophrenia and psychotic and nonpsychotic major depression. The American journal of psychiatry 148(5), 612–616. [PubMed: 2018162]

Marin D, Madotto E, Fabbro F, Skrap M, Tomasino B, 2017 Design fluency and neuroanatomical correlates in 54 neurosurgical patients with lesions to the right hemisphere. Journal of neuro-oncology 135(1), 141–150. [PubMed: 28677108]

McIntosh AM, Munoz Maniega S, Lymer GK, McKirdy J, Hall J, Sussmann JE, Bastin ME, Clayden JD, Johnstone EC, Lawrie SM, 2008 White matter tractography in bipolar disorder and schizophrenia. Biological psychiatry 64(12), 1088–1092. [PubMed: 18814861]

Miller M, Banerjee A, Christensen G, Joshi S, Khaneja N, Grenander U, Matejic L, 1997 Statistical methods in computational anatomy. Statistical methods in medical research 6(3), 267–299. [PubMed: 9339500]

Miller MI, Faria AV, Oishi K, Mori S, 2013 High-throughput neuro-imaging informatics. Frontiers in neuroinformatics 7, 31. [PubMed: 24381556]

Miller MI, Qiu A, 2009 The emerging discipline of Computational Functional Anatomy. NeuroImage 45(1 Suppl), S16–39. [PubMed: 19103297]

Mitelman SA, Torosjan Y, Newmark RE, Schneiderman JS, Chu KW, Brickman AM, Haznedar MM, Hazlett EA, Tang CY, Shihabuddin L, Buchsbaum MS, 2007 Internal capsule, corpus callosum and long associative fibers in good and poor outcome schizophrenia: a diffusion tensor imaging survey. Schizophrenia research 92(1–3), 211–224. [PubMed: 17329081]

Mori S, Oishi K, Faria AV, 2009 White matter atlases based on diffusion tensor imaging. Curr Opin Neurol 22(4), 362–369. [PubMed: 19571751]

Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl P, Mazziotta J, 2008 Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. NeuroImage 40(2), 570–582. [PubMed: 18255316]

Mori S, Wu D, Ceritoglu C, Li Y, Kolasny A, Valliant MA, faria AV, Oishi K, Miller MI, 2016 MRICloud: Delivering High-Throughput MRI Neuroinformatics as Cloud-Based Software as a Service. Comput. Sci. Eng 18(21), 15.

Nazeri A, Chakravarty MM, Felsky D, Lobaugh NJ, Rajji TK, Mulsant BH, Voineskos AN, 2013 Alterations of superficial white matter in schizophrenia and relationship to cognitive performance. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 38(10), 1954–1962. [PubMed: 23591167]

Oestreich LK, Lyall AE, Pasternak O, Kikinis Z, Newell DT, Savadjiev P, Bouix S, Shenton ME, Kubicki M, Whitford TJ, McCarthy-Jones S, 2017 Characterizing white matter changes in chronic schizophrenia: A free-water imaging multi-site study. Schizophrenia research.

Oishi K, Faria A, Jiang H, Li X, Akhter K, Zhang J, Hsu JT, Miller MI, van Zijl PC, Albert M, Lyketsos CG, Woods R, Toga AW, Pike GB, Rosa-Neto P, Evans A, Mazziotta J, Mori S, 2009 Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. NeuroImage 46(2), 486–499. [PubMed: 19385016]

Oishi K, Faria AV, van Ziji PCM, Mori S, 2011 MRI atlas of human white matter, Second ed. Elsevier.

Pagel T, Baldessarini RJ, Franklin J, Baethge C, 2013 Characteristics of patients diagnosed with schizoaffective disorder compared with schizophrenia and bipolar disorder. Bipolar Disord 15(3), 229–239. [PubMed: 23528024]

Perez-Iglesias R, Tordesillas-Gutierrez D, Barker GJ, McGuire PK, Roiz-Santianez R, Mata I, de Lucas EM, Quintana F, Vazquez-Barquero JL, Crespo-Facorro B, 2010a White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging. NeuroImage 49(1), 199–204. [PubMed: 19619664]

Perez-Iglesias R, Tordesillas-Gutierrez D, McGuire PK, Barker GJ, Roiz-Santianez R, Mata I, de Lucas EM, Rodriguez-Sanchez JM, Ayesa-Arriola R, Vazquez-Barquero JL, Crespo-Facorro B, 2010b White matter integrity and cognitive impairment in first-episode psychosis. The American journal of psychiatry 167(4), 451–458. [PubMed: 20160006]

Pini S, Cassano GB, Dell'Osso L, Amador XF, 2001 Insight into illness in schizophrenia, schizoaffective disorder, and mood disorders with psychotic features. The American journal of psychiatry 158(1), 122–125. [PubMed: 11136644]

Price G, Cercignani M, Parker GJ, Altmann DR, Barnes TR, Barker GJ, Joyce EM, Ron MA, 2007 Abnormal brain connectivity in first-episode psychosis: a diffusion MRI tractography study of the corpus callosum. NeuroImage 35(2), 458–466. [PubMed: 17275337]

Price G, Cercignani M, Parker GJ, Altmann DR, Barnes TR, Barker GJ, Joyce EM, Ron MA, 2008 White matter tracts in first-episode psychosis: a DTI tractography study of the uncinate fasciculus. NeuroImage 39(3), 949–955. [PubMed: 17988894]

Radomsky ED, Haas GL, Mann JJ, Sweeney JA, 1999 Suicidal behavior in patients with schizophrenia and other psychotic disorders. The American journal of psychiatry 156(10), 1590–1595. [PubMed: 10518171]

Rink L, Pagel T, Franklin J, Baethge C, 2016 Characteristics and heterogeneity of schizoaffective disorder compared with unipolar depression and schizophrenia - a systematic literature review and meta-analysis. Journal of affective disorders 191, 8–14. [PubMed: 26599364]

Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y, 2012 Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. Brain structure & function 217(2), 503–515. [PubMed: 21909706]

Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y, 2013 White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. Frontiers in neuroscience 7, 32. [PubMed: 23493587]

Schmidt A, Lenz C, Smieskova R, Harrisberger F, Walter A, Riecher-Rossler A, Simon A, Lang UE, McGuire P, Fusar-Poli P, Borgwardt SJ, 2015 Brain Diffusion Changes in Emerging Psychosis and the Impact of State-Dependent Psychopathology. Neuro-Signals 23(1), 71–83. [PubMed: 26682550]

Tang X, Yoshida S, Hsu J, Huisman TA, Faria AV, Oishi K, Kutten K, Poretti A, Li Y, Miller MI, Mori S, 2014 Multi-contrast multi-atlas parcellation of diffusion tensor imaging of the human brain. PloS one 9(5), e96985. [PubMed: 24809486]

Tartaglia MC, Zhang Y, Racine C, Laluz V, Neuhaus J, Chao L, Kramer J, Rosen H, Miller B, Weiner M, 2012 Executive dysfunction in frontotemporal dementia is related to abnormalities in frontal white matter tracts. Journal of neurology 259(6), 1071–1080. [PubMed: 22037958]

Tsuang D, Coryell W, 1993 An 8-year follow-up of patients with DSM-III-R psychotic depression, schizoaffective disorder, and schizophrenia. The American journal of psychiatry 150(8), 1182–1188. [PubMed: 8328561]

Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD, 2008 Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. NeuroImage 42(2), 1032–1044. [PubMed: 18602840]

Voineskos AN, Lobaugh NJ, Bouix S, Rajji TK, Miranda D, Kennedy JL, Mulsant BH, Pollock BG, Shenton ME, 2010 Diffusion tensor tractography findings in schizophrenia across the adult lifespan. Brain : a journal of neurology 133(Pt 5), 1494–1504. [PubMed: 20237131]

Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR, 2013 Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain : a journal of neurology 136(Pt 6), 1692–1707. [PubMed: 23649697]

Wang Q, Deng W, Huang C, Li M, Ma X, Wang Y, Jiang L, Lui S, Huang X, Chua SE, Cheung C, McAlonan GM, Sham PC, Murray RM, Collier DA, Gong Q, Li T, 2011 Abnormalities in connectivity of white-matter tracts in patients with familial and non-familial schizophrenia. Psychological medicine 41(8), 1691–1700. [PubMed: 21205362]

Whitford TJ, Kubicki M, Schneiderman JS, O'Donnell LJ, King R, Alvarado JL, Khan U, Markant D, Nestor PG, Niznikiewicz M, McCarley RW, Westin CF, Shenton ME, 2010 Corpus callosum abnormalities and their association with psychotic symptoms in patients with schizophrenia. Biological psychiatry 68(1), 70–77. [PubMed: 20494336]

Williams OA, Zeestraten EA, Benjamin P, Lambert C, Lawrence AJ, Mackinnon AD, Morris RG, Markus HS, Charlton RA, Barrick TR, 2017 Diffusion tensor image segmentation of the cerebrum provides a single measure of cerebral small vessel disease severity related to cognitive change. NeuroImage. Clinical 16, 330–342. [PubMed: 28861335]

Wilmsmeier A, Ohrmann P, Suslow T, Siegmund A, Koelkebeck K, Rothermundt M, Kugel H, Arolt V, Bauer J, Pedersen A, 2010 Neural correlates of set-shifting: decomposing executive functions in schizophrenia. Journal of psychiatry & neuroscience : JPN 35(5), 321–329. [PubMed: 20731964]

Woods SW, 2003 Chlorpromazine equivalent doses for the newer atypical antipsychotics. The Journal of clinical psychiatry 64(6), 663–667. [PubMed: 12823080]

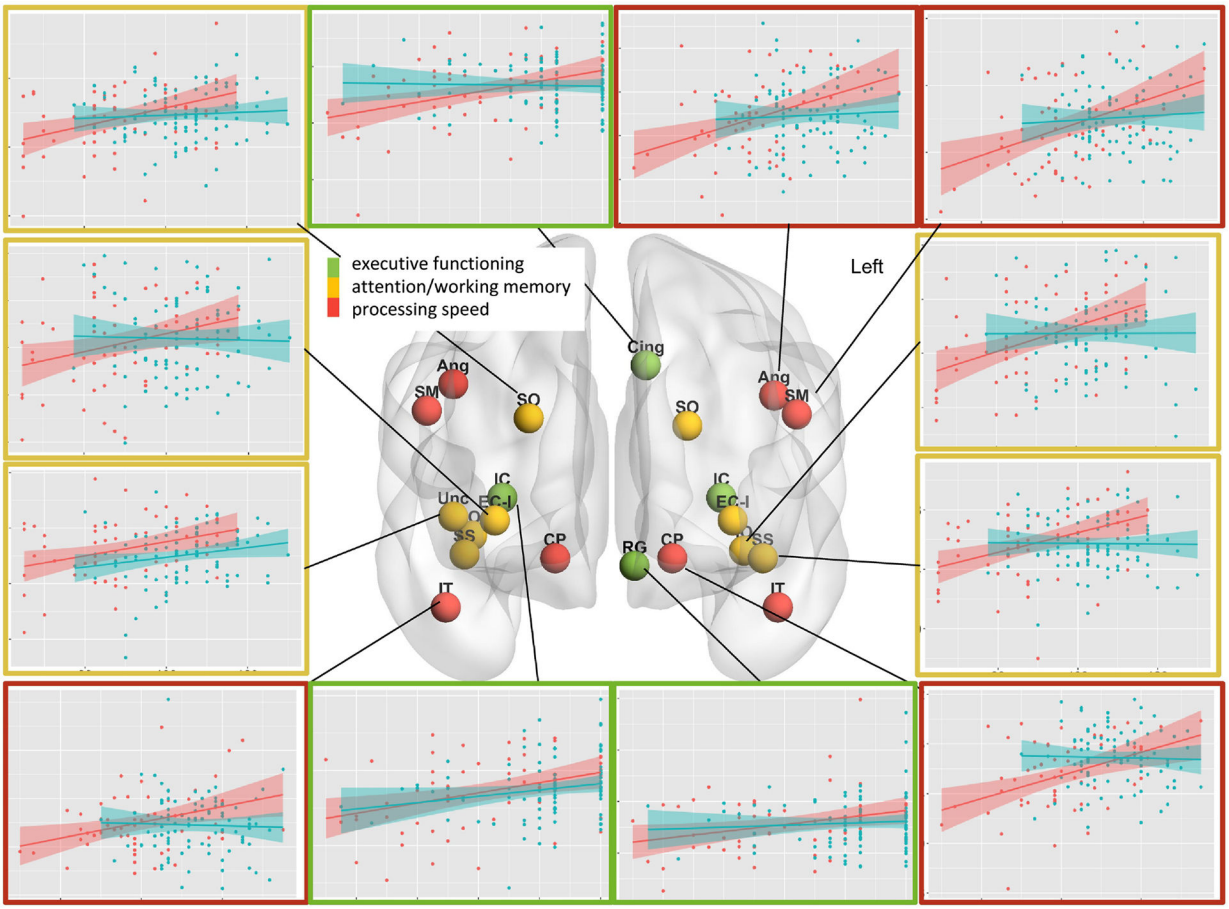

Figure 1:

Correlations between regional fractional anisotropy and cognitive scores. The type of cognitive test is color-coded on the spheres overlaid in the anatomical areas on the glass brain, and in the scatterplot frames (red: processing speed, yellow: attention / working memory, green: executive functioning). In the scatterplots, red are S-FEP participants and blue are controls; the shadow represents the 95% interval for the linear fitting (line); y-axis is FA [0.35–0.5]; x-axis is cognitive score [60–130]. Significant correlations between fractional anisotropy and cognition were found in patient's group, but not in controls, in the white matter adjacent to the following gyrus: angular (Ang), supramarginal (SM), superior and inferior occipital (SO, IO), fusiform (Fu), middle and inferior temporal (MT, IT), rectus (RG), superior frontal (SF), and insula, which was considered in combination with external capsula (EC-I), as well as in the internal capsule (IC), sagittal striatum (SS), and cerebral peduncle (CP). The brain is visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

Table 1:

Demographic and neuropsychological summary

		mean (± standard deviation)				*p*-value			
		HC (n=93)	**FEP (n=82)**	**S-FEP (n=58)**	**M-FEP (n=24)**	**HC x FEP**	**HC x S-FEP**	**HC x M-FEP**	**S-FEP x M-FEP**
Age (years)		23.3±4.5	22.5±4.2	22.5±4.2	23.1±5	0.2	0.17	0.77	0.57
Gender (M / F)		41/52	57/25	46/12	12/12	**<0.0001**	**<0.0001**	0.6	**0.017**
Race (aa/as/c/h/o)		57/2/29/4/1	40/5/31/3/3	32/2/21/1/2	9/2/10/2/1	0.4	0.5	0.12	**0.007**
Antipsychotic dose *			356.9±285.9	368.7±303.7	332.2±248.3				0.6
Processing speed	no adj.	113.4±9.3	102.3±12.4	105.3±10.7	114.6±4.2	**<0.0001**	**<0.0001**	**0.001**	0.08
	adjusted	108.8±15.1	87.9±19.0	90.9±18.4	108.5±4.8	**<0.0001**	**<0.0001**	**<0.0001**	0.223
Attention / working memory	no adj.	103.7±11.1	92.7±14.6	99.3±11.7	103.1±7.5	**<0.0001**	**<0.0001**	0.11	**0.003**
	adjusted	104.1±14.5	87.4±18.2	94.4±15.7	102.5±12.6	**<0.0001**	**<0.0001**	**0.007**	**0.01**
Verbal learning memory	no adj.	106.1±12.0	93.0±14.5	98.8±13.2	94.4±14.5	**<0.0001**	**<0.0001**	**0.02**	**0.019**
	adjusted	103.8±14.3	87.5±16.4	92.5±15.4	89.2±18.9	**<0.0001**	**<0.0001**	**0.003**	**0.049**
Visual learning memory	no adj.	111.8±10.5	102.1±13.6	105.6±13.7	106.3±12.3	**<0.0001**	**<0.0001**	0.11	0.132
	adjusted	103.5±14.1	88.6±17.4	92.3±18.7	92.5±13.6	**<0.0001**	**<0.0001**	**0.026**	0.226
Ideational fluency	no adj.	106.1±10.1	94.5±13.3	100.5±13.2	91.7±12.4	**<0.0001**	**<0.0001**	**0.049**	**0.015**
	adjusted	111.9±12.0	95.4±16.8	101.6±16.9	93.7±15.2	**<0.0001**	**<0.0001**	**0.008**	**0.045**
Executive functioning	no adj.	101.2±9.5	93.0±12.5	98.5±9.3	95±17.4	**<0.0001**	**<0.0001**	0.5	**0.004**
	adjusted	101.8±13.6	88.5±17.5	94.8±13.3	91.7±24.4	**<0.0001**	**<0.0001**	0.08	**0.017**

Race codes: aa: african american, as: asian, c: caucasian, h: hispanic, o: others

S-FEP: schizophrenia and schizoaffective disorders; M-FEP: major depression and bipolar disorder with psychiatric features. HC: healthy controls. Adjusted / no adj. refers to adjustment of cognitive scores for age, gender, and race

*Antipsychotic medication dosage information was unavailable for six patients.

Table 2:

Differences in fractional anisotropy (FA) between FEP (and subgroups) and controls (HC), paired by age, gender, and race.

	mean FA				*p*-value (*p*-multiple comparisons corrected)		
	HC	**FEP**	**S-FEP**	**M-FEP**	**HC x FEP**	**HC x S-FEP**	**HC x M-FEP**
Cerebral peduncles	0.670	0.653	0.654	0.649	<0.0001(<0.0001)	<0.0001(<0.0001)	<0.0001(<0.0001)
Corpus callosum	0.610	0.593	0.597	0.585	<0.0001(<0.0001)	<0.0001 (0.002)	<0.0001(<0.0001)
Projection fibers at pons level	0.552	0.539	0.536	0.545	<0.0001(<0.0001)	<0.0001(<0.0001)	0.084 (0.3)
Caudate	0.220	0.233	0.236	0.223	<0.0001 (0.003)	<0.0001 (0.002)	0.412(0.6)
Internal capsule	0.636	0.626	0.626	0.628	<0.0001 (0.003)	0.001 (0.007)	0.003 (0.045)
Inferior occipital-frontal fasciculus	0.445	0.435	0.438	0.430	0.003 (0.022)	0.042 (0.2)	0.006 (0.05)
Anterior corona radiata	0.433	0.427	0.428	0.425	0.02 (0.048)	0.045 (0.3)	0.029(0.16)
Total white matter	0.456	0.452	0.453	0.450	0.005 (0.025)	0.047 (0.2)	0.005 (0.05)

Table 3:

Summary of correlations between cognitive tests and fractional anisotropy (FA) in FEP, S-FEP, and healthy controls (HC). Correlations were accessed using the cognitive test scores, ("cog. score"), as well as the scores adjusted for age, gender, and race ("adj. cog. score"). "R^2adj" and "P" are the r squared adjusted and p-value for the linear model fitting the correlation between regional FA and cognition; "P-mv" is the p-value for the partial correlation between regional FA and cognition, including age, race, gender, and antipsychotic dosage as covariates; "P-gr.sl." is the *p*-value for the difference between the group slopes (S-FEP vs. controls, or FEP vs. controls).

			Processing Speed				Attention / Working Memory						Executive Functioning	
			Cerebral peduncle	Inferior temporal	Angular left	Supramarginal Left	Superior occipital	Inferior occipital	Sagittal striatum	External capsule / Insula	Uncinate right	Cingulum left	Rectus left	Retrolenticular int. capsule right	Sagittal striatum right
S-FEP	cog. score	R^2adj	0.164	0.121	0.155	0.153	0.174	0.135	0.14	0.124	0.093	0.146	0.075	0.118	0.159
		P	0.001	0.004	0.001	0.001	0.001	0.003	0.002	0.004	0.012	0.002	0.021	0.005	0.001
		P-mv	0.001	0.01	0.0002	0.002	0.001	0.004	0.0004	0.0009	0.021	0.0003	0.002	0.0009	0.001
		P-gr.sl.	0.003	0.005	0.012	0.016	0.003	0.004	0.005	0.006	0.43	0.006	0.089	0.18	0.051
	adj. cog. score	R^2adj	0.216	0.146	0.185	0.121	0.148	0.092	0.134	0.147	0.103	0.122	0.095	0.101	0.132
		P	0.0001	0.002	0.0005	0.004	0.002	0.012	0.003	0.002	0.008	0.004	0.011	0.009	0.003
		P-mv	0.0007	0.008	0.0001	0.005	0.003	0.005	0.0004	0.0005	0.012	0.0004	0.004	0.0005	0.0008
		P-gr.sl.	0.003	0.002	0.002	0.004	0.029	0.002	0.025	0.005	0.09	0.018	0.042	0.06	0.064
FEP	cog. score	R^2adj	0.129	0.085	0.088	0.111	0.133	0.066	0.049	0.117	0.094	0.107	0.039	0.07	0.049
		P	0.0002	0.004	0.003	0.001	0.0007	0.01	0.023	0.001	0.002	0.001	0.038	0.008	0.023
		P-mv	0.0002	0.004	0.001	0.0009	0.0006	0.006	0.004	0.0007	0.0146	0.0005	0.02	0.003	0.048
		P-gr.sl.	0.003	0.015	0.04	0.049	0.011	0.026	0.04	0.008	0.43	0.01	0.222	0.286	0.334
	adj. cog. score	R^2adj	0.145	0.085	0.091	0.072	0.11	0.039	0.044	0.122	0.073	0.109	0.06	0.068	0.032
		P	0.0001	0.004	0.003	0.007	0.001	0.039	0.029	0.001	0.007	0.001	0.013	0.009	0.038
		P-mv	0.0002	0.003	0.001	0.003	0.001	0.007	0.003	0.005	0.009	0.0005	0.022	0.003	0.048
		P-gr.sl.	0.008	0.009	0.01	0.022	0.016	0.009	0.034	0.0004	0.137	0.027	0.181	0.127	0.377
HC	cog. score	R^2adj	−0.011	−0.01	−0.004	−0.011	−0.01	−0.005	−0.01	−0.009	0.021	−0.005	−0.006	0.028	0.001
		P	0.93	0.764	0.446	0.955	0.74	0.458	0.835	0.686	0.089	0.815	0.486	0.058	0.31
		P-mv	0.72	0.651	0.465	0.557	0.588	0.539	0.848	0.204	0.512	0.822	0.408	0.125	0.474
	adj. cog. score	R^2adj	−0.01	−0.011	−0.005	−0.004	−0.01	0.01	−0.009	0.017	−0.007	−0.001	−0.001	0.005	−0.003
		P	0.754	0.862	0.477	0.436	0.818	0.163	0.719	0.108	0.54	0.629	0.344	0.233	0.395
		P-mv	0.746	0.607	0.556	0.43	0.523	0.769	0.95	0.154	0.582	0.838	0.447	0.163	0.514