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

Andreia V. Faria [a,*], Jeffrey Crawford [b], Chenfei Ye [f], Johnny Hsu [a], Anshel Kenkare [b], David Schretlen [a,b], Akira Sawa [b,c,d,e]

[a] Department of Radiology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] Department Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Department of Biomedical Engineering, The Johns Hopkins University, Baltimore, MD, USA
[d] Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
[e] Department of Mental Health, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA
[f] Department of Electronics and Information, Harbin Institute of Technology Shenzhen Graduate School, Guangdong, China

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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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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., 2018; 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 et al., 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

* Corresponding author at: Magnetic Resonance Research Division, Department of Radiology, The Johns Hopkins University School of Medicine, 217B Traylor Bldg., 720 Rutland Ave., Baltimore, MD 21205, USA.
E-mail address: afaria1@jhmi.edu (A.V. Faria).

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criteria, demographics, and clinical features can be found elsewhere (Kamath et al., 2018, 2019). 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 3 T 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 1).

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, 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). S-FEP 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 (Table 1).

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 × FEP	HC × S-FEP	HC × M-FEP	S-FEP × 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[a]			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.

[a] Antipsychotic medication dosage information was unavailable for six patients.

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