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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).

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

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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.

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 × FEP	HC × S-FEP	HC × 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)

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 Fig. 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 Fig. 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.

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Conflict of interest
The authors declare no conflict of interest.

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.
DS: collected data; contributed data.
AS: conceived the analysis; wrote the paper.

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. ccore	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 sc	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

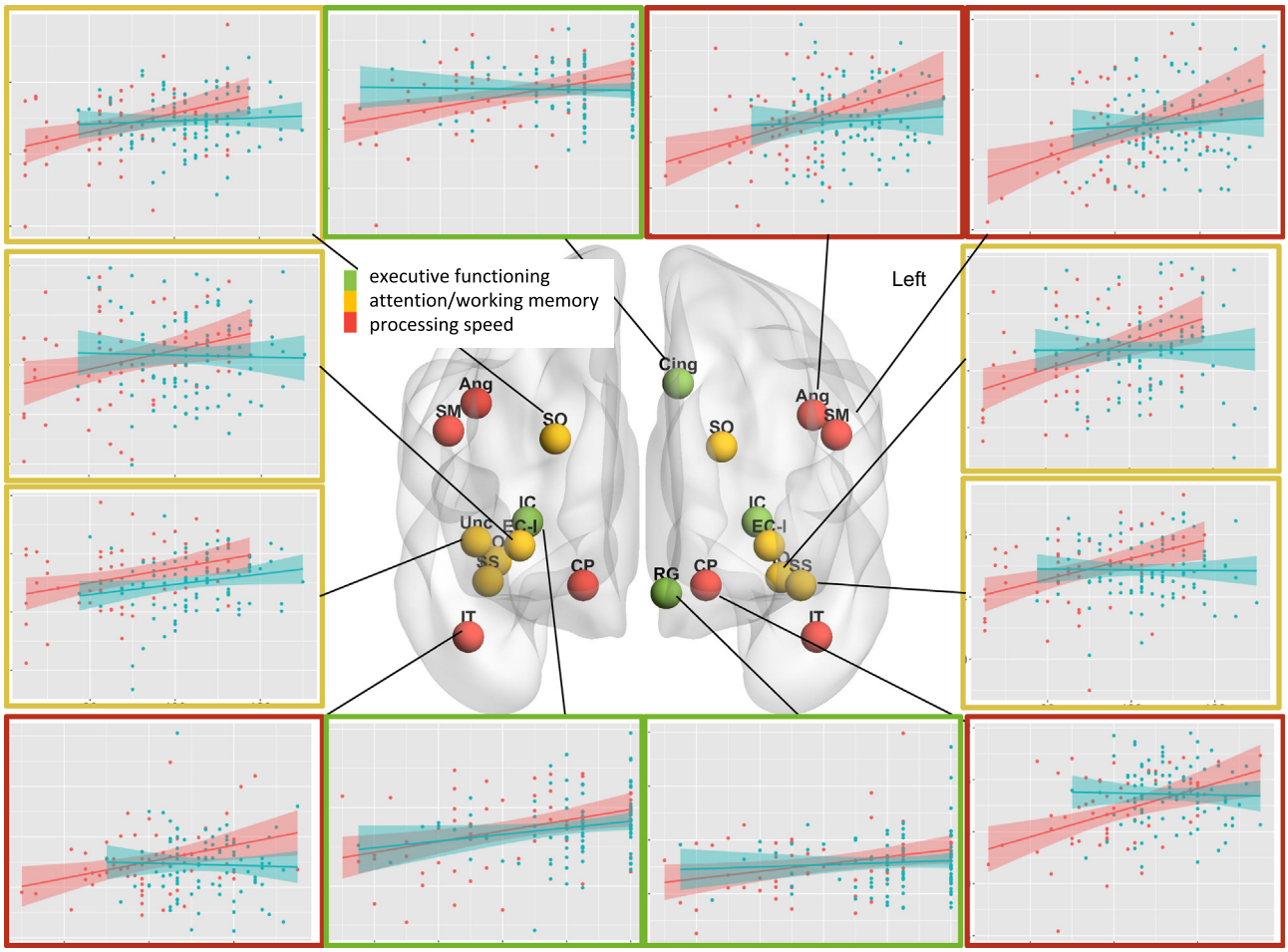

Fig. 1. Legend: Correlations between regional fractional anisotropy and cognitive scores. The type of cognitive test is color-coded on the spheres overlaid in the anatomical areas on the glass brain, and in the scatterplot frames (red: processing speed, yellow: attention / working memory, green: executive 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/).

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