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White Matter Alterations Between Brain Network Hubs Underlie Processing Speed Impairment in Patients With Schizophrenia

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Processing speed (PS) impairment is one of the most severe and common cognitive deficits in schizophrenia. Previous studies have reported correlations between PS and white matter diffusion properties, including fractional anisotropy (FA), in several fiber bundles in schizophrenia, suggesting that white matter alterations could underpin decreased PS. In schizophrenia, white matter alterations are most prevalent within inter-hub connections of the rich club. However, the spatial and topological characteristics of this association between PS and FA have not been investigated in patients. In this context, we tested whether structural connections comprising the rich club network would underlie PS impairment in 298 patients with schizophrenia or schizoaffective disorder and 190 healthy controls from the Australian Schizophrenia Research Bank. PS, measured using the digit symbol coding task, was largely (Cohen's $d = 1.33$) and significantly ($P < .001$) reduced in the patient group when compared with healthy controls. Significant associations between PS and FA were widespread in the patient group, involving all cerebral lobes. FA was not associated with other cognitive measures of phonological fluency and verbal working memory in patients, suggesting specificity to PS. A topological analysis revealed that despite being spatially widespread, associations between PS and FA were over-represented among connections forming the rich club network. These findings highlight the need to consider brain network topology when investigating high-order cognitive functions that may be spatially distributed among several brain regions. They also reinforce the evidence that brain hubs and their interconnections may be particularly vulnerable parts of the brain in schizophrenia.

Key words: psychosis/digit symbol coding/fractional anisotropy/white matter/MRI/rich club

Introduction

Processing speed (PS) impairment is pervasive across schizophrenia,[1–5] and represents a fundamental cognitive problem that underpins higher-level cognition and mediates other cognitive differences between schizophrenia and controls.[1,2,6] PS impairment is already evident in individuals at clinical high risk for psychosis,[7–11] where it is associated with poor functional outcomes[12,13] and risk of conversion to psychosis.[14–16] In patients with first episode psychosis[4,6,17–19] and chronic schizophrenia,[20,21] it is present to an even greater extent.

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Larger effect sizes are evident for between-group differences in PS relative to other cognitive impairments,[1,22] especially when measured using the digit symbol coding task.[2] This PS impairment occurs independent of antipsychotic medication use[18,21] and is recognized as a key predictor of low autonomy[20] and poor clinical outcome in schizophrenia.[17] There is evidence that it could also represent an endophenotype of schizophrenia[20,23,24] that is distinct from PS impairment associated with aging.[25] Despite this extensive characterization of PS at the level of behavior in schizophrenia, the underlying neural correlates of PS impairment in patients are not well-defined.

Widespread white matter alterations in schizophrenia[26] could provide the neural basis of PS impairment in patients. Numerous studies indicate that PS either associates with white matter fractional anisotropy (FA) in schizophrenia[27–30] or mediates the association between FA and other indices like working memory[31] or general intelligence.[32] In the first episode psychosis, correlations between white matter FA and cognition, including PS, are stronger in those who develop schizophrenia than those who develop a mood disorder.[33] Accordingly, the correlation coefficient between PS and FA in a given white matter fiber bundle is associated with the severity of white matter alterations (ie, effect size of patient vs control FA group comparison) in the same fiber bundle of patients with chronic schizophrenia.[31] Together, these data reinforce the idea that alterations of white matter FA and PS impairments are closely related in schizophrenia.

Positive correlations between PS and white matter FA have been reported in the main white matter tracts, including inter-hemispheric commissural fibers[27,29] and several association pathways (eg, cingulum, corona radiata, and inferior occipito-frontal fasciculus)[28,29] in patients with schizophrenia. Indeed, associations between PS and white matter alterations in schizophrenia tend to be evident between vulnerable regions (ie, those showing progressive connectivity alterations following a first psychotic episode), a majority of which are ranked among the most central nodes and which constitute the brain's so-called rich club.[22]

The rich club is an organizational property of the brain's architecture that supports the integrative processing required for higher brain functions including cognition.[34] Organization of the rich club results from the tendency of central "nodes" or "hubs" (ie, brain regions) to be more densely connected to other hub regions than expected by chance, enabling fast communication pathways between remote and functionally segregated brain regions.[35] In schizophrenia, despite there being a spatially widespread decrease of FA in white matter, these alterations topologically converge on connections between hub regions of the cerebral network (ie, the rich club).[36,37] Damage to the rich club has more diffuse and less specific functional consequences than damage to topologically peripheral components of the network.[38] This suggests that white matter alterations in the rich club could underpin cognitive impairments in schizophrenia, including PS. However, there is no study that has investigated both the spatial and topological properties of associations between PS and white matter FA in a large sample of patients with schizophrenia. Previously reported associations between PS and FA averaged from the entire white matter skeleton or a priori selected white matter fiber bundles could not identify the spatial characteristics of this association (ie, widespread, or specific to certain brain regions). Moreover, the importance of brain network topology, and more particularly the integrity of connections that make up the rich club, in maintaining PS performance was never assessed.

We aimed to overcome this research gap using data from schizophrenia patients and healthy controls in the Australian Schizophrenia Research Bank. The novel contributions of this work include identification of anatomical characteristics of the association between white matter alterations and processing speed as well as establishment of a link between rich-club topology and processing speed in schizophrenia. Previous work in the same cohort has revealed both PS impairments of large magnitude,[39–41] as well as white matter alterations that are spatially widespread but topologically converge on inter-hub connections of the rich club.[36] However, the relationship between PS impairment and FA alterations has not been investigated in this cohort, particularly their spatial and topological relationships. In this context, we first hypothesized that white matter regions showing a correlation between PS and FA in patients would be spatially widespread, but more prevalent within inter-hub connections of the rich club than outlying areas. Second, we hypothesized that this correlation would be limited to scores from the digit symbol coding task, a cognitive test which is relatively specific to PS and central to cognitive impairment in schizophrenia.[1,2]

Materials and Methods

This study was approved by the Melbourne Health Human Research Ethics Committee (Project ID: 2010.250). All participants provided written informed consent for the analysis of their data.

Participants

Schizophrenia and control participants were recruited into the Australian Schizophrenia Research Bank (ASRB) from 5 Australian states and territories (ie, Brisbane, Melbourne, Newcastle, Perth, and Sydney) from 2008 to 2013. Further details pertaining to ASRB protocols and participant recruitment can be found elsewhere.[42] Briefly, English speaking participants aged between 18 and 65 years were recruited through medical facilities and national media campaigns. Patients were included

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if they had a confirmed diagnosis of schizophrenia or schizoaffective disorder, based on DSM-IV criteria. Exclusion criteria included any organic brain disorder, history of severe brain trauma, movement disorders, current drug or alcohol dependence, and electroconvulsive therapy in the past 6 months. Control participants were also excluded if they had any personal or family history of psychosis or bipolar I disorder. Participants were selected from a diffusion neuroimaging sample used in a previous study[36] (n = 326 patients and n = 197 healthy controls) if a PS value was available. This resulted in 298 patients and 190 healthy controls for the current study.

Demographics and Clinical Assessment

Symptoms were assessed with the Diagnostic Interview for Psychosis (DIP)[43] and the Scale for the Assessment of Negative Symptoms (SANS).[44] Information regarding the type of medication used in the past month was self-reported by patients.

Cognitive Assessment

PS was assessed using the digit symbol coding (DSC) test, in which participants are asked to sequentially pair specific numbers with given geometric figures, following a printed key during a 90-s period. DSC score corresponds to the number of correct symbols coded within the allowed time. Assessments of verbal working memory and phonological fluency were also included in this study to examine, in a secondary analysis, the specificity of associations between FA and PS. These assessments respectively included the letter-number sequencing (LNS) test, in which participants were required to mentally sort random series of numbers and letters into numerical order followed by alphabetical order, and the Controlled Oral Word Association test (F-A-S version), in which participants were required to produce as many words beginning with the letters F, then A and S over three 60-s trials. LNS score corresponds to the number of correct responses out of 21 items. F-A-S score indicates the average number of correct answers within the allocated time. For each of the 3 tests, higher score means better cognitive performance. Full scale intelligence quotient (IQ) was estimated using the 2-subscale (i.e., Matrix reasoning and Vocabulary) from the Wechsler Abbreviated Scale of Intelligence (WASI).[45]

Image Acquisition

The same model of 1.5 Tesla MRI machine (ie, Siemens Avanto) and diffusion-weighted MR acquisition sequence were used across the 5 scanning sites. A total of 64 unique gradient directions distributed on the half-sphere were acquired using a spin-echo EPI sequence with the following parameters: b value, 1000 s/mm^2; 65 consecutive axial slices of thickness 2.4 mm; 104 × 104 image matrix with an in-plane voxel resolution of 2.4 × 2.4 mm; field of view, 25 × 25 cm; repetition time, 8.4/8.5 s; echo time, 88 ms; and flip angle, 90°. A T2-weighted (ie, b = 0) volume and a T1-weighted anatomical image (ie, magnetization-prepared rapid acquisition gradient echo) were also acquired before the acquisition of the diffusion-weighted volumes.

Image Processing

Processing of the diffusion-weighted images, diffusion tractography, and rich club delineation followed exactly the same procedures and software used in our earlier work in this cohort.[36]

Fractional Anisotropy

Affine registration of diffusion-weighted images (DWI) to T2-weighted volumes was performed to correct for distortions and head movements (eddy_correct command in FSL 5.0.7, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and gradient tables were rotated accordingly using an in-house script for MATLAB version 2011a (MathWorks). Diffusion tensors were fitted to DWI using least squares estimation, enabling the computation of fractional anisotropy (FA) maps in MRtrix 0.2.12 (http://www.nitrc.org/projects/mrtrix/) for each participant. FA maps were normalized to MNI standard space using the sequential use of FLIRT and FNIRT commands with default parameters as implemented in FSL 5.0.7 for the registration of FA images. FA maps were smoothed with a Gaussian kernel of SD = 1 mm. Quality check included a visual inspection of each FA map for gross abnormalities and/or artifacts. Two participants were excluded due to registration failure.

Diffusion Tractography

For each participant, 1 million streamlines were seeded in all the white matter and propagated using a deterministic algorithm before being registered to MNI space using standard procedures and parameters in MRtrix 0.2.12. Using an in-house script for Matlab, FA was averaged across all voxels traversed by a valid connection linking a pair of regions comprising the 116-node Automated Anatomical Labeling atlas.[46] A connection was considered as valid if at least 1 voxel was traversed by at least 5 streamlines at the subject level and if the connection was present in at least 10% of subjects at the group level.[47] The structural connectivity between pairs of regions was thus quantified using the average FA along the interregional fiber bundle delineated with tractography. This led to a 116×116 connectivity matrix for each individual.

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Rich Club Delineation

The rich club refers to a densely interconnected network of brain hubs, which arises from the propensity of richly connected hub regions to preferentially form structural connections with other hub regions.[35] In the present study, the rich club was based on a binary network comprising connections that were consistently identified across the group (ie, "valid" connections as previously specified). The rich club was then defined as the subgraph comprising connections between pairs of nodes with more than k edges (ie, node degree > k). To quantify the extent of richness, a rich club coefficient was calculated by dividing the number of edges in this subgraph by the total possible number of edges in the same subgraph. This rich club coefficient was calculated for different k values ranging from 30 to 50 and then compared with the coefficients obtained in 100 surrogate networks generated by the degree-preserving Maslov–Sneppen randomization procedure,[48] as implemented in the Brain Connectivity Toolbox.[49]

Analyses

Distributions for age and WASI were not normal in both groups, and thus range was reported instead of SD, and nonparametric Mann–Whitney t-test was used for group comparisons. Fisher's exact test was used to compare the proportion of males and females between groups. DSC, F-A-S, and LNS showed a normal distribution and a standard parametric t-test was used for group comparisons. Voxel-based analyses were conducted in schizophrenia and control group separately using Randomise (FSL 6.0.1) to test whether FA in white matter was significantly correlated with PS (ie, DSC). If this primary analysis was significant, other cognitive measures (ie, LNS, F-A-S) were tested in secondary analyses to investigate the specificity of the association. An inclusive mask (ie, FMRIB58_FA_1mm template from FSL, thresholded at 2500) was used to restrict statistical testing to white matter voxels. Age, sex, and scanning site were included as nuisance factors in the general linear model. We used the Threshold-Free Cluster Enhancement method, a nonparametric cluster-based procedure based on permutations (ie, 10,000) to correct for Type I errors.[50] For the primary analysis (ie, correlation of FA with DSC) and the secondary analyses (ie, correlations of FA with LNS or F-A-S), only clusters with $P < .05$ (familywise error corrected) were considered significant. Connectivity analyses used the network-based statistic (NBS)[51] to test whether structural connectivity, as measured with tract-averaged FA, correlated with DSC in a primary analysis and LNS or F-A-S in secondary analyses. Schizophrenia and control group were tested separately. Age, sex, and scanning site were set as nuisance factors in the model. Subnetworks were considered significant if their corrected P values were < .05 at the whole-network level, using a preliminary t-statistic threshold of 3 ($P = .001$) and 10,000 permutations. The connectogram illustrated in figure 4 was generated with NeuroMArVL (https://immersive.erc.monash.edu/neuromarvl).

Results

Demographics

The results of schizophrenia and control group comparisons are presented in Table 1. There were significantly more males in the schizophrenia group compared to controls. Estimated full scale IQ and cognitive test

Table 1. Demographics

	Controls	Patients	p value (Cohen's d)
	n = 190	n = 298	
Age	41.5 (18–65)	38 (20–65)	.17
Sex (Males; Females)	95/95	206/92	**< .001**
WASI	119 (80–138)	105 (63–133)	**< .001**
Digit symbol coding	56 (28–89)	42 (13–72)	**< .001 (1.33)**
F-A-S	14.3 (5–27)	11.5 (0–21.7)	**< .001 (0.84)**
Letter-number sequencing	12 (5–20)	10 (2–18)	**< .001 (1.01)**
Positive symptoms	—	8 (0–18)	—
Negative symptoms	—	25 (0–85)	—
Illness duration	—	14 (1–47)	—
Diagnosis (SCZA; SCZP)	—	48; 250	—
Taking typical antipsychotics	—	31 (10%)	—
Taking atypical antipsychotics	—	244 (82%)	—
Taking antidepressants	—	89 (30%)	—

Note: If not otherwise specified, the values represent the median and the range is given in brackets. Age and illness duration are given in years. Averaged phonological fluency scores for letters F, A, and S (F-A-S). Negative symptoms score = total score from the Scale for the Assessment of Negative Symptoms (SANS), data were unavailable for 13 cases; Positive symptoms score = sum of lifetime hallucinations and lifetime delusions from the Diagnostic Interview for Psychosis (DIP), data were unavailable for 32 cases; Schizoaffective disorder (SCZA); Schizophrenia (SCZP); Wechsler Abbreviated Scale of Intelligence (WASI).

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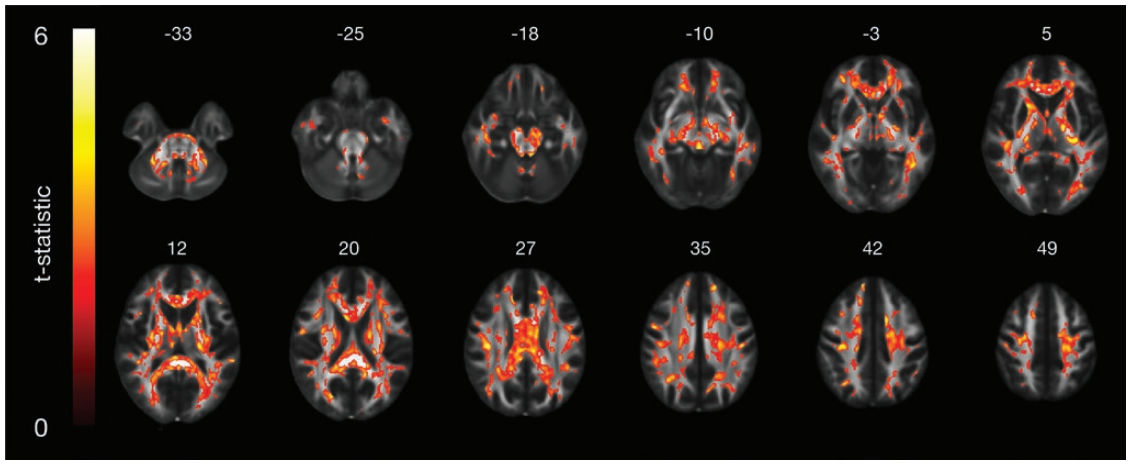

Fig. 1. Widespread correlation between fractional anisotropy and digit symbol coding performance in patients with schizophrenia. All coloured voxels are significant at the whole-brain level (non-parametric, familywise error corrected $P < .05$). Effect size at each voxel is quantified with the *t*-statistic and represented in a series of axial brain slices. Z coordinates are shown at the top of each slice. The colour bar indicates the *t*-statistic (0.1–6.1). Right side of the brain is on the left side of the figure.

scores (ie, DSC, LNS, and F-A-S) were all significantly lower in the patient group. DSC was significantly higher in females (M = 58.46, SD = 10.24) than in males (M = 53.28, SD = 10.75) in the control group ($P < .001$) but there was no significant difference regarding DSC between males and females in the schizophrenia group. DSC was still significantly lower in schizophrenia than in control group when males (41.20 ±10.56 vs 53.28 ±10.75; $P < .001$) and females (42.41 ±10.8 vs 58.46±10.24; $P < .001$) were tested independently. There was no effect of antipsychotics on PS (ie, DSC was not statistically different between patients taking [M = 41.58, SD = 10.27] or not taking [M = 41.59, SD = 12.83] antipsychotics).

Correlation With White Matter Pathology

In the schizophrenia group, DSC was positively correlated with FA in a widespread cluster that encompassed most of the white matter mask (166,224 voxels; corrected $P < .05$; figures 1 and 2). Secondary analyses indicated no significant association between FA and the two other cognitive measures (ie, whole brain voxel-based analyses with LNS and F-A-S) in the schizophrenia group, indicating the relative specificity of the association between PS deficit and white matter pathology. In healthy controls, DSC was not significantly associated with FA. Association between DSC and FA still remained after the inclusion of negative symptoms (ie, total from the SANS) and positive symptoms (sum of lifetime hallucinations and lifetime delusions from the DIP) scores as additional covariates in our model.

Correlation With Connectivity Disruptions

In the schizophrenia group, DSC was significantly associated with tract-averaged FA in a widespread subnetwork comprising 1,503 (36%) of the 4,230 unique pairs of

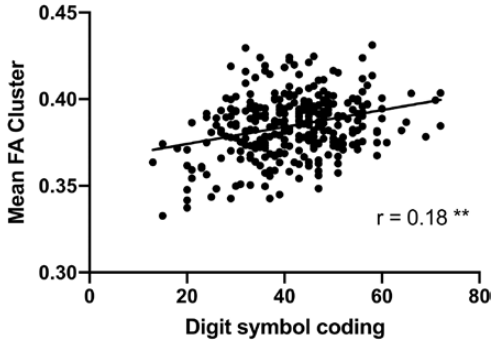

Fig. 2. Illustration of the positive correlations between fractional anisotropy values averaged from voxels comprising the significant cluster and digit symbol coding scores in patients with schizophrenia. Partial correlation *r* (ie, age, sex, and site regressed out) is provided. $^{**}P = .002$.

regions tested (corrected $P < .05$). However, we found no significant association between tract-average FA and LNS or F-A-S in the schizophrenia group, again indicating the relative specificity of the association between PS and connectivity disruptions. In healthy controls, DSC was not significantly associated with tract-averaged FA.

Association Between Rich Club and Processing Speed

The structural brain networks mapped for the schizophrenia group, which had a sparsity measure of 42.4%, showed evidence of rich club organization. Quantitatively, the rich club coefficient for nodal degrees between k = 30 to k = 50 was significantly higher in the patient group than what would be expected to emerge by chance under the null hypothesis of randomly rewired networks ($P < .05$) (figure 3A). Additionally, we observed that the relative involvement of inter-hub connections in the rich club where FA correlated with DSC was higher than it would have been only by chance (ie, 100 permutations) for

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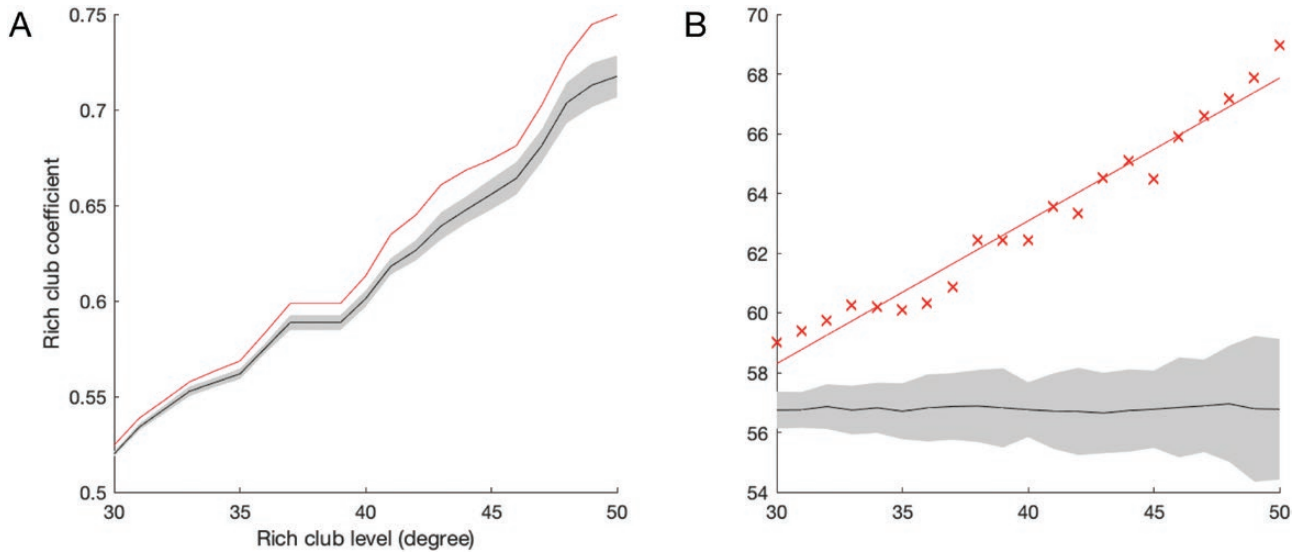

Fig. 3. Altered connectivity linked to processing speed impairments specifically relates to inter-hub connections of the rich club. (A) Presence of a rich club organization in the group of schizophrenia patients. For nodal degree from 30 to 50, the rich club coefficient in the patients (red line) is different from null data generated by degree-preserving randomisation (black line with shaded area representing its confidence interval for $\alpha = 0.5$). (B) Red crosses represent the proportion of inter-hub connections in the rich club, which are associated with reduced processing speed. Precise numerical values are 58.3% ($k = 30$), 60.7% ($k = 35$), 63.1% ($k = 40$), 65.5% ($k = 45$), and 67.9% ($k = 50$). The best fit (red line) is statistically higher than null data (ie, randomly rewired networks; black line with shaded area representing the confidence interval for $\alpha = 0.5$) for nodal degree ranging from 30 to 50.

nodal degree 30 to 50 ($P < .05$) (figure 3B). This indicates that connectivity impairments underlying PS deficits in patients tend to concentrate in inter-hub connections of the rich club, while relatively sparing more peripheral connections of the network. Inter-hub connections ($n = 555$) of the rich club ($k = 50$) showing a significant correlation between the mean FA along their path and DSC in patients are represented in the connectogram illustrated in figure 4. An interactive version of the connectogram is also available online (https://immersive.erc.monash.edu/neuromarvl/?save=87c06a7b-c9b4-47b7-8186-736c5530703f_128.250.0.136).

Discussion

Among the many domains of cognition that are disturbed in schizophrenia, impaired PS is the most robust and has the largest effect size.[1,2] Similarly, widespread FA alterations in white matter in schizophrenia are well replicated findings.[26] Although relationships between PS and white matter FA have been reported in many white matter bundles individually, to date, there has been no investigation of PS and FA at the whole brain level in a large sample. In addition, although the topological organization of the cerebral network and especially the rich club has been shown to be most severely impacted in schizophrenia,[36,37] its link with PS impairments has yet to be demonstrated.

In the present study, voxel-based and tract-based analyses at the whole brain level revealed that approximately a third of the total white matter volume and white matter connections showed a correlation between FA and PS in patients with schizophrenia but not in healthy controls. This correlation with FA was relatively specific to PS as we did not find any correlation between FA and the two other cognitive measures (ie, phonological fluency [F-A-S] or verbal working memory [LNS]) in patients. Further, we found that white matter connections showing a correlation between FA and PS in patients were more likely to be involved in inter-hub connections of the rich club.

Among the cognitive domains implicated in schizophrenia, PS is the one that has been associated the most often with measures of white matter alterations, including FA, in patients with this illness.[27–32,52] The absence of correlations between LNS or F-A-S and FA in this study confirms this specific association and suggests that FA alterations could represent a biomarker of PS impairment in patients.

Despite several reports of positive correlations between FA and PS in healthy controls,[53–56] this association seems to be particularly related to aging.[57–61] Hence, the absence of association between PS and FA in our control group is most likely due to the relatively young age of our control participants (median = 41.5 years).

The significant positive correlation between the severity of white matter alterations and the degree of PS deficit in both voxel-based and tract-based analyses raises the possibility that PS might be a simple surrogate marker of clinical severity. However, previous analyses in this cohort found no relationship between FA and positive or negative symptom scores.[36] The absence of

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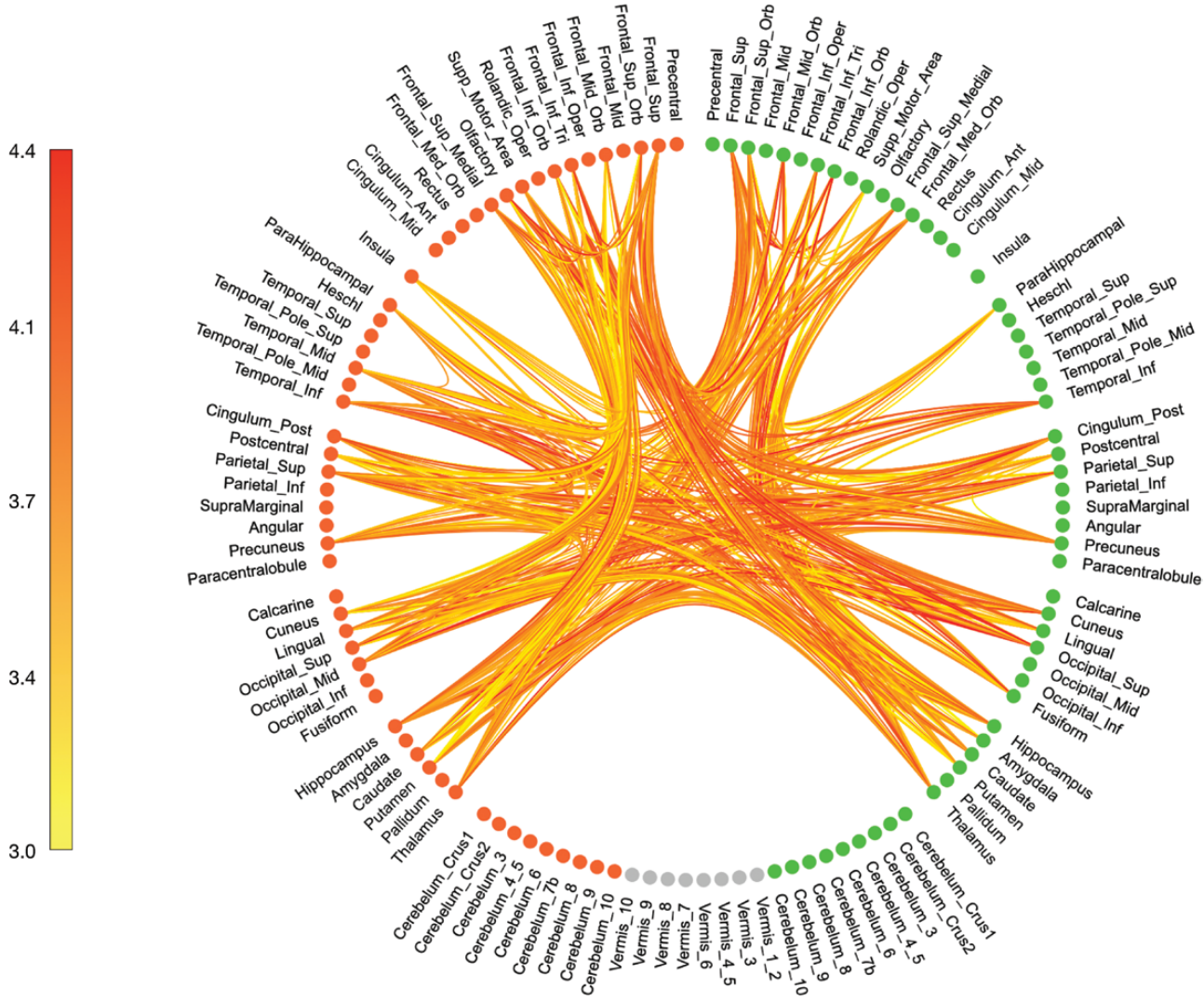

Fig. 4. Connectogram of disrupted white matter tracts comprising the rich club and associated with processing speed impairments in patients with schizophrenia. All nodes (regions from the aal atlas) are represented but only edges comprising the rich club ($k = 50$) and showing a significant correlation (non-parametric corrected $P < .05$) between the mean FA along their path and digit symbol coding task in patients are represented. *t*-statistic for each edge is given by its color (yellow to red). Left hemisphere structures are represented on the left (red dots) and right hemisphere structures on the right (green dots).

association between FA and symptomatic expression in schizophrenia was also confirmed in a large meta-analysis from ENIGMA consortium where only trends between FA and symptom scores were reported.[26] Finally, the widespread association between PS and FA remained when positive and negative symptom scores were set as covariates in the model.

The involvement of the rich club for associations between PS deficit and white matter alterations is in accordance with previous studies highlighting the importance of the dysconnectivity between hubs in schizophrenia. Indeed, connectivity has been shown to be disproportionally altered between hubs in patients with schizophrenia compared with controls,[36,37] and to a lesser degree in their unaffected relatives, leading to a more segregated network.[62] Despite a strong implication of the fronto-parietal network in the rich club, hubs are spatially dispersed across the whole brain.[34] Rich club organization of the brain network supports complex brain dynamics like the balance between integration and segregation of information, two fundamental properties allowing high order cognitive functions and behavior.[63] Indeed, inter-hub connections are necessary for the integration of information between different systems which are distant in space.[64]

This study is not only the first reporting that associations between PS deficit and white matter alterations specifically involve inter-hub connections in schizophrenia, but it also highlights the importance of the integrity of large-scale cerebral networks for proper integrative functions

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and high-order cognition. Accordingly, associations between reduced PS and altered connectivity between rich club nodes have also been reported in several other brain pathologies including small vessel disease,[65] multiple sclerosis,[66] and late depression.[67]

Inter-hub connections have long maturational trajectories and tend to display distinctive properties of microstructural organization (ie, higher FA) and myelination (ie, higher magnetic transfer ratio).[68] Hubs show higher rates of changes (ie, cortical shrinkage, myelination, and transcriptional profile) than peripheral nodes during adolescence.[69] Hubs also exhibit high oxidative metabolism,[68] which could expose them to oxidative stress and inflammation, two interdependent parameters suspected to have a central role in the pathophysiology of schizophrenia.[70,71] All these characteristics make inter-hub connections particularly vulnerable to stressors during development, but also later in life.[72]

Vulnerability of the rich club can also be due to shared genetic factors. For instance, recent work indicates that the strength of connectivity between hubs is highly heritable[73] and that interconnected hubs show tightly coupled gene expression, especially for genes related to oxidative metabolism[74] and genes related to schizophrenia.[69] In general, brain disorders tend to affect brain hubs in particular[75] and white matter impairments tend to concentrate on rich or feeder connections.[76] This cross-disorder involvement of the rich club might explain overlapping cognitive comorbidities between schizophrenia and other psychiatric disorders, but also the heterogeneity of clinical presentations in patients with schizophrenia.[76]

The alleged role of oxidative stress in the topological distribution of white matter alterations associated with PS impairment in schizophrenia is also suggested by several findings from our group. Indeed, N-acetylcysteine (NAC), an antioxidant, was shown to improve not only PS[77] but also structural (ie, FA)[78] and functional[79] connectivity in patients with early psychosis.

Among the limitations of the study is the lack of available data regarding the time-course and dosage of medication used by the participants, which did not allow us to assess the effects of antipsychotic treatment and its possible role in the correlation between FA and PS. However, the association between PS and antipsychotics has been mostly highlighted in patients with low IQ.[19] In our study, only 4 of our group of 298 patients had an IQ below 70, potentially minimizing the impact of medication (and low IQ) in the present work. This is further exemplified by our finding of no PS difference between patients currently taking or not taking an antipsychotic medication. Another limitation is the obvious overlap in cognitive domains between neuropsychological tasks. While the DSC test is complex enough to measure more than just psychomotor performance (eg. as is done with the finger-tapping task), it is also simple enough to minimize the effect of other high-order cognitive functions.[80–82] However, DSC cannot separate cognitive from motor slowing and there may be other deficits (eg, spatial short-term memory or spatial working memory impairment) that impair DSC performance in patients with schizophrenia.[83,84] In general, even the absence of an association between FA and LNS or F-A-S cannot completely rule out the possibility of a partial effect of cognitive functions other than PS in the association between FA and DSC. Regarding brain network analysis, it may be that FA estimates are less susceptible to noise effect for white matter tracts comprising the rich club, compared with peripheral tracts, potentially explaining the abundance of rich-club connections associated with processing speed. However, further work would be required to understand tract-specific variation in imaging noise. Finally, while the same type of scanner and acquisition was used at each site, image harmonization methods could be used in the future to further minimize the impact of potential site differences on FA and tractography.

In conclusion, we reported that white matter FA alterations associated with the most robust differences in cognitive impairment in schizophrenia, namely, PS, are topologically distributed within the central components of the brain network. This suggests that considering the topological rather than the spatial organization of the brain could be a more sensitive method to link certain measures of cognition with their biological substrate. From a pathophysiological perspective, it is likely that the vulnerability of between-hub connections is related to their central role in brain integration flow, their important metabolic activity, and their vulnerability to oxidative stress and inflammation.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Knowles EE, David AS, Reichenberg A. Processing speed deficits in schizophrenia: reexamining the evidence. *Am J Psychiatry.* 2010;167(7):828–835.
2. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry.* 2007;64(5):532–542.
3. Schatz J. Cognitive processing efficiency in schizophrenia: generalized vs domain specific deficits. *Schizophr Res.* 1998;30(1):41–49.
4. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology.* 2009;23(3):315–336.
5. Carruthers SP, Van Rheenen TE, Gurvich C, Sumner PJ, Rossell SL. Characterising the structure of cognitive heterogeneity in schizophrenia spectrum disorders. A systematic review and narrative synthesis. *Neurosci Biobehav Rev.* 2019;107:252–278.
6. Andersen R, Fagerlund B, Rasmussen H, *et al.* The influence of impaired processing speed on cognition in first-episode antipsychotic-naïve schizophrenic patients. *Eur Psychiatry.* 2013;28(6):332–339.
7. Seidman LJ, Giuliano AJ, Meyer EC, *et al.*; North American Prodrome Longitudinal Study (NAPLS) Group. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Arch Gen Psychiatry.* 2010;67(6):578–588.
8. Kelleher I, Murtagh A, Clarke MC, Murphy J, Rawdon C, Cannon M. Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: support for the processing speed hypothesis. *Cogn Neuropsychiatry.* 2013;18(1-2):9–25.
9. Carrión RE, McLaughlin D, Goldberg TE, *et al.* Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry.* 2013;70(11):1133–1142.
10. Haining K, Matrunola C, Mitchell L, *et al.* Neuropsychological deficits in participants at clinical high risk for psychosis recruited from the community: relationships to functioning and clinical symptoms. *Psychol Med.* 2020;50(1):77–85.
11. Fusar-Poli P, Deste G, Smieskova R, *et al.* Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry.* 2012;69(6):562–571.
12. Lin A, Wood SJ, Nelson B, *et al.* Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophr Res.* 2011;132(1):1–7.
13. Niendam TA, Bearden CE, Zinberg J, Johnson JK, O'Brien M, Cannon TD. The course of neurocognition and social functioning in individuals at ultra high risk for psychosis. *Schizophr Bull.* 2007;33(3):772–781.
14. Pukrop R, Klosterkötter J. Neurocognitive indicators of clinical high-risk states for psychosis: a critical review of the evidence. *Neurotox Res.* 2010;18(3-4):272–286.
15. Michel C, Ruhrmann S, Schimmelmann BG, Klosterkötter J, Schultze-Lutter F. A stratified model for psychosis prediction in clinical practice. *Schizophr Bull.* 2014;40(6):1533–1542.
16. Catalan A, Salazar de Pablo G, Aymerich C *et al.* Neurocognitive Functioning in Individuals at Clinical High Risk for Psychosis. *JAMA Psychiatry.* 2021
17. Leeson VC, Barnes TR, Harrison M, *et al.* The relationship between IQ, memory, executive function, and processing speed in recent-onset psychosis: 1-year stability and clinical outcome. *Schizophr Bull.* 2010;36(2):400–409.
18. Olivier MR, Killian S, Chiliza B, *et al.* Cognitive performance during the first year of treatment in first-episode schizophrenia: a case-control study. *Psychol Med.* 2015;45(13):2873–2883.
19. Ballesteros A, Sánchez-Torres AM, López-Ilundain JM, *et al.*; PEPs Group. Is cognitive impairment associated with antipsychotic dose and anticholinergic equivalent loads in first-episode psychosis? *Psychol Med.* 2018;48(13):2247–2256.
20. Sánchez P, Ojeda N, Peña J, *et al.* Predictors of longitudinal changes in schizophrenia: the role of processing speed. *J Clin Psychiatry.* 2009;70(6):888–896.
21. Bonner-Jackson A, Grossman LS, Harrow M, Rosen C. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. *Compr Psychiatry.* 2010;51(5):471–479.
22. Griffa A, Baumann PS, Klauser P, *et al.* Brain connectivity alterations in early psychosis: from clinical to neuroimaging staging. *Transl Psychiatry.* 2019;9(1):62.
23. Glahn DC, Almasy L, Blangero J, *et al.* Adjudicating neurocognitive endophenotypes for schizophrenia. *Am J Med Genet B Neuropsychiatr Genet.* 2007;144B(2):242–249.
24. Osborne KJ, Walther S, Shankman SA, Mittal VA. Psychomotor slowing in schizophrenia: implications for endophenotype and biomarker development. *Biomark Neuropsychiatry.* 2020;2:100016.
25. Mathias SR, Knowles EEM, Barrett J, *et al.* The processing-speed impairment in psychosis is more than just accelerated aging. *Schizophr Bull.* 2017;43(4):814–823.
26. Kelly S, Jahanshad N, Zalesky A, *et al.* Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Mol Psychiatry.* 2018;23(5):1261–1269.
27. Kochunov P, Rowland LM, Fieremans E, *et al.* Diffusion-weighted imaging uncovers likely sources of processing-speed deficits in schizophrenia. *Proc Natl Acad Sci U S A.* 2016;113(47):13504–13509.
28. Rigucci S, Rossi-Espagnet C, Ferracuti S, *et al.* Anatomical substrates of cognitive and clinical dimensions in first episode schizophrenia. *Acta Psychiatr Scand.* 2013;128(4):261–270.
29. Karbasforoushan H, Duffy B, Blackford JU, Woodward ND. Processing speed impairment in schizophrenia is mediated by white matter integrity. *Psychol Med.* 2015;45(1):109–120.
30. Liu X, Lai Y, Wang X, *et al.* Reduced white matter integrity and cognitive deficit in never-medicated chronic schizophrenia: a diffusion tensor study using TBSS. *Behav Brain Res.* 2013;252:157–163.
31. Kochunov P, Coyle TR, Rowland LM, *et al.* Association of white matter with core cognitive deficits in patients with schizophrenia. *JAMA Psychiatry.* 2017;74(9):958–966.
32. Alloza C, Cox SR, Duff B, *et al.* Information processing speed mediates the relationship between white matter and general

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intelligence in schizophrenia. *Psychiatry Res Neuroimaging.* 2016;254:26–33.
33. Faria AV, Crawford J, Ye C, *et al.* Relationship between neuropsychological behavior and brain white matter in first-episode psychosis. *Schizophr Res.* 2019;208:49–54.
34. Sporns O. Contributions and challenges for network models in cognitive neuroscience. *Nat Neurosci.* 2014;17(5): 652–660.
35. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. *J Neurosci.* 2011;31(44): 15775–15786.
36. Klauser P, Baker ST, Cropley VL, *et al.* White Matter Disruptions in Schizophrenia Are Spatially Widespread and Topologically Converge on Brain Network Hubs. *Schizophr Bull.* 2017;43(2):425–435.
37. van den Heuvel MP, Sporns O, Collin G, *et al.* Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA Psychiatry.* 2013;70(8):783–792.
38. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. *Nat Rev Neurosci.* 2015;16(3):159–172.
39. Green MJ, Cairns MJ, Wu J, *et al.*; Australian Schizophrenia Research Bank. Genome-wide supported variant MIR137 and severe negative symptoms predict membership of an impaired cognitive subtype of schizophrenia. *Mol Psychiatry.* 2013;18(7):774–780.
40. Green MJ, Chia TY, Cairns MJ, *et al.*; Australian Schizophrenia Research Bank. Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *J Psychiatr Res.* 2014;49:43–50.
41. Wells R, Swaminathan V, Sundram S, *et al.* The impact of premorbid and current intellect in schizophrenia: cognitive, symptom, and functional outcomes. *NPJ Schizophr.* 2015;1:15043.
42. Loughland C, Draganic D, McCabe K, *et al.* Australian Schizophrenia Research Bank: a database of comprehensive clinical, endophenotypic and genetic data for aetiological studies of schizophrenia. *Aust N Z J Psychiatry.* 2010;44(11):1029–1035.
43. Castle DJ, Jablensky A, McGrath JJ, *et al.* The diagnostic interview for psychoses (DIP): development, reliability and applications. *Psychol Med.* 2006;36(1):69–80.
44. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry.* 1982;39(7):784–788.
45. Wechsler D. *Manual for the Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation; 1999.
46. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* 2002;15(1):273–289.
47. de Reus MA, van den Heuvel MP. Estimating false positives and negatives in brain networks. *Neuroimage.* 2013;70:402–409.
48. Maslov S, Sneppen K. Specificity and stability in topology of protein networks. *Science.* 2002;296(5569):910–913.
49. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* 2010;52(3):1059–1069.
50. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* 2009;44(1):83–98.
51. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage.* 2010;53(4):1197–1207.
52. Zeng B, Ardekani BA, Tang Y, *et al.* Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. *Schizophr Res.* 2016;172(1-3):1–8.
53. Oschwald J, Mérillat S, Liem F, Röcke C, Martin M, Jäncke L. Lagged coupled changes between white matter microstructure and processing speed in healthy aging: a longitudinal investigation. *Front Aging Neurosci.* 2019;11:298.
54. Hidese S, Ota M, Matsuo J, *et al.* Correlation between the wechsler adult intelligence scale- 3 rd edition metrics and brain structure in healthy individuals: a whole-brain magnetic resonance imaging study. *Front Hum Neurosci.* 2020;14:211.
55. Madole JW, Ritchie SJ, Cox SR, *et al.* Aging-Sensitive networks within the human structural connectome are implicated in late-life cognitive declines. *Biol Psychiatry.* 2021;89(8):795–806.
56. Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *Neuroimage.* 2008;42(2):1032–1044.
57. Penke L, Maniega SM, Bastin ME, *et al.* Brain white matter tract integrity as a neural foundation for general intelligence. *Mol Psychiatry.* 2012;17(10):1026–1030.
58. Penke L, Muñoz Maniega S, Murray C, *et al.* A general factor of brain white matter integrity predicts information processing speed in healthy older people. *J Neurosci.* 2010;30(22):7569–7574.
59. Salami A, Eriksson J, Nilsson LG, Nyberg L. Age-related white matter microstructural differences partly mediate age-related decline in processing speed but not cognition. *Biochim Biophys Acta.* 2012;1822(3):408–415.
60. Koch K, Wagner G, Schachtzabel C, *et al.* Age-dependent visuomotor performance and white matter structure: a DTI study. *Brain Struct Funct.* 2013;218(5):1075–1084.
61. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Front Neurosci.* 2013;7:32.m
62. van den Heuvel MP, Fornito A. Brain networks in schizophrenia. *Neuropsychol Rev.* 2014;24(1):32–48.
63. Deco G, Tononi G, Boly M, Kringelbach ML. Rethinking segregation and integration: contributions of whole-brain modelling. *Nat Rev Neurosci.* 2015;16(7):430–439.
64. Hagmann P, Cammoun L, Gigandet X, *et al.* Mapping the structural core of human cerebral cortex. *PLoS Biol.* 2008;6(7):e159.
65. Tuladhar AM, Lawrence A, Norris DG, Barrick TR, Markus HS, de Leeuw FE. Disruption of rich club organisation in cerebral small vessel disease. *Hum Brain Mapp.* 2017;38(4):1751–1766.
66. Stellmann JP, Hodecker S, Cheng B, *et al.* Reduced rich-club connectivity is related to disability in primary progressive MS. *Neurol Neuroimmunol Neuroinflamm.* 2017;4(5):e375.
67. Mai N, Zhong X, Chen B, *et al.* Weight Rich-Club analysis in the white matter network of late-life depression with memory deficits. *Front Aging Neurosci.* 2017;9:279.

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68. Collin G, Sporns O, Mandl RC, van den Heuvel MP. Structural and functional aspects relating to cost and benefit of rich club organization in the human cerebral cortex. *Cereb Cortex.* 2014;24(9):2258–2267.
69. Whitaker KJ, Vértes PE, Romero-Garcia R, *et al.*; NSPN Consortium. Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. *Proc Natl Acad Sci U S A.* 2016;113(32):9105–9110.
70. Hardingham GE, Do KQ. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. *Nat Rev Neurosci.* 2016;17(2):125–134.
71. Steullet P, Cabungcal JH, Monin A, *et al.* Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A "central hub" in schizophrenia pathophysiology? *Schizophr Res.* 2016;176(1):41–51.
72. Bullmore E, Sporns O. The economy of brain network organization. *Nat Rev Neurosci.* 2012;13(5):336–349.
73. Arnatkeviciute A, Fulcher BD, Oldham S, *et al.* Genetic influences on hub connectivity of the human connectome. *Nat Commun.* 2021;12(1):4237.
74. Fulcher BD, Fornito A. A transcriptional signature of hub connectivity in the mouse connectome. *Proc Natl Acad Sci U S A.* 2016;113(5):1435–1440.
75. Crossley NA, Mechelli A, Scott J, *et al.* The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain.* 2014;137(Pt 8):2382–2395.
76. Griffa A, Van den Heuvel MP. Rich-club neurocircuitry: function, evolution, and vulnerability. *Dialogues Clin Neurosci.* 2018;20(2):121–132.
77. Conus P, Seidman LJ, Fournier M, *et al.* N-acetylcysteine in a double-blind randomized placebo-controlled trial: toward biomarker-guided treatment in early psychosis. *Schizophr Bull.* 2018;44(2):317–327.
78. Klauser P, Xin L, Fournier M, *et al.* N-acetylcysteine add-on treatment leads to an improvement of fornix white matter integrity in early psychosis: a double-blind randomized placebo-controlled trial. *Transl Psychiatry.* 2018;8(1):220.
79. Mullier E, Roine T, Griffa A, *et al.* N-Acetyl-Cysteine Supplementation Improves Functional Connectivity Within the Cingulate Cortex in Early Psychosis: A Pilot Study. *Int J Neuropsychopharmacol.* 2019;22(8):478–487.
80. Salthouse TA. The processing-speed theory of adult age differences in cognition. *Psychol Rev.* 1996;103(3):403–428.
81. Jensen AR. Why is reaction time correlated with psychometric G. *Curr Dir Psychol Sci.* 1993;2:53–56.
82. Wechsler D. *WAIS-R manual: Wechsler adult intelligence scale-revised.* New York: Psychological Corporation; 1981.
83. Pantelis C, Barnes TR, Nelson HE, *et al.* Frontal-striatal cognitive deficits in patients with chronic schizophrenia. *Brain.* 1997;120 (Pt 10):1823–1843.
84. Pantelis C, Barnes TRE, Nelson HE. Is the concept of frontal–subcortical dementia relevant to schizophrenia. *Br J Psychiatry.* 1992;160:442–460.

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