

Processing speed impairment in schizophrenia is mediated by white matter integrity

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Background. Processing speed predicts functional outcome and is a potential endophenotype for schizophrenia. Establishing the neural basis of processing speed impairment may inform the treatment and etiology of schizophrenia. Neuroimaging investigations in healthy subjects have linked processing speed to brain anatomical connectivity. However, the relationship between processing speed impairment and white matter (WM) integrity in schizophrenia is unclear.

Method. Individuals with schizophrenia and healthy subjects underwent diffusion tensor imaging (DTI) and completed a brief neuropsychological assessment that included measures of processing speed, verbal learning, working memory and executive functioning. Group differences in WM integrity, inferred from fractional anisotropy (FA), were examined throughout the brain and the hypothesis that processing speed impairment in schizophrenia is mediated by diminished WM integrity was tested.

Results. WM integrity of the corpus callosum, cingulum, superior and inferior frontal gyri, and precuneus was reduced in schizophrenia. Average FA in these regions mediated group differences in processing speed but not in other cognitive domains. Diminished WM integrity in schizophrenia was accounted for, in large part, by individual differences in processing speed.

Conclusions. Cognitive impairment in schizophrenia was mediated by reduced WM integrity. This relationship was strongest for processing speed because deficits in working memory, verbal learning and executive functioning were not mediated by WM integrity. Larger sample sizes may be required to detect more subtle mediation effects in these domains. Interventions that preserve WM integrity or ameliorate WM disruption may enhance processing speed and functional outcome in schizophrenia.

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Introduction

Schizophrenia is characterized by widespread neuropsychological impairment (Heinrichs & Zakzanis, 1998; Dickinson *et al.* 2008). Among the specific domains affected, processing speed is the most impaired, with patients performing approximately 1.5 standard deviations below healthy comparison subjects on average (Dickinson *et al.* 2007). Processing speed impairment is an important predictor of functional outcome in patients, may predict conversion to a full-blown psychotic disorder in at-risk subjects, and is also present in unaffected relatives of probands (Dickinson *et al.* 2007; Sanchez *et al.* 2009; Nuechterlein *et al.* 2011; Fusar-Poli *et al.* 2012). Consequently, elucidating the

neural basis of processing speed impairment has the potential to improve our understanding of the etiology and treatment of schizophrenia.

Given the nature of neuropsychological tests of processing speed, which require subjects to rapidly perform relatively simple tasks that integrate several basic cognitive operations, it is not surprising that neuroimaging investigations of the neural basis of processing speed have focused on anatomical brain connectivity. In healthy subjects, processing speed is associated with white matter (WM) integrity, inferred from fractional anisotropy (FA) quantified with diffusion tensor imaging (DTI), in several brain areas, including pre-frontal WM, longitudinal fasciculus, external capsule, optic radiation, cingulum and corpus callosum (Tuch *et al.* 2005; Turken *et al.* 2008; Kerchner *et al.* 2012; Salami *et al.* 2012; Koch *et al.* 2013; Sasson *et al.* 2013). Some of these associations seem to be specific to processing speed. For instance, WM integrity in the cingulum, corpus callosum and corona radiata has been reliably linked to processing speed whereas correlations

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between WM integrity and executive functions and memory are often limited to frontal and temporal lobe regions respectively (Bendlin *et al.* 2010; Sasson *et al.* 2013). However, there is also evidence that WM integrity throughout the brain is related to processing speed and, more broadly, intellectual functioning (Penke *et al.* 2010, 2012).

Evidence of widespread reductions in WM integrity in schizophrenia provides a possible neural basis for processing speed impairment (Melonakos *et al.* 2011; Fitzsimmons *et al.* 2013; Yao *et al.* 2013). Numerous WM regions/tracts have been implicated in schizophrenia, including the corpus callosum, cingulum and longitudinal fasciculus. However, the findings are remarkably heterogeneous, raising the possibility that WM disruption in schizophrenia may vary as a function of individual differences in cognitive impairment. Emerging evidence suggests that this is indeed the case as the integrity of several WM tracts, including the cingulum, uncinate fasciculus, longitudinal fasciculi, internal capsule and thalamocortical connections, has been linked to several cognitive abilities, including processing speed, working memory, executive functioning and verbal memory (Nestor *et al.* 2004, 2010; Szczekko *et al.* 2007; Karlsgodt *et al.* 2008; Qiu *et al.* 2009; Takei *et al.* 2009; Perez-Iglesias *et al.* 2010; Levitt *et al.* 2012; Marenco *et al.* 2012; Voineskos *et al.* 2013). Nevertheless, several questions remain unaddressed. First, the extent to which cognitive impairment, especially slowed processing speed, is mediated by WM integrity remains unclear. Second, the specificity of cognition–WM associations has not been established. Third, it is not known if disrupted WM integrity in schizophrenia is entirely attributable to cognitive impairment. That is, is there a categorical ‘disease’ effect on WM integrity, or does variation along the dimension of cognition account for altered WM integrity in schizophrenia? We explored these questions using tract-based spatial statistics (TBSS; Smith *et al.* 2006) analysis of DTI data and neuropsychological testing. In light of strong evidence that processing speed in particular is related to WM integrity in healthy subjects, we tested the hypothesis that processing speed impairment in schizophrenia is mediated by diminished WM integrity and that this relationship is would be strongest for processing speed compared to other cognitive domains. We further explored the extent to which cognitive impairment accounts for reduced WM integrity in schizophrenia.

Method

Participants and study procedures

Twenty-six schizophrenia/schizo-affective patients and 20 healthy subjects were recruited to participate in

this study, which was approved by the Vanderbilt University Institutional Review Board. All subjects provided written informed consent prior to participation. Individuals with schizophrenia were recruited from the Psychotic Disorders Program at the Vanderbilt Psychiatric Hospital in Nashville, TN. Healthy subjects were recruited from Nashville and surrounding area by print/internet advertisement and by word of mouth. All study participants were administered the SCID (First *et al.* 1996) to confirm diagnoses in patients and rule out current or past psychiatric illness in healthy subjects. Exclusion criteria included: age <18 years or >60 years; estimated pre-morbid IQ<70; presence of a systemic medical illness or neurological disorder that would affect study results; reported pregnancy or lactation; history of significant head trauma; psychotropic drug use (healthy controls only); substance abuse within the past 3 months (patients); lifetime history of substance abuse/dependence (healthy controls); and magnetic resonance imaging (MRI) contraindicators (e.g. metal implants, claustrophobia).

Neuropsychological testing

Subjects completed the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001), a single-word reading test of estimated pre-morbid intellectual functioning, and the Screen for Cognitive Impairment in Psychiatry (SCIP; Purdon, 2005). The SCIP is a brief cognitive battery that includes five subtests: (1) a word-list learning test of verbal memory comprising three learning trials of a 10-word list; (2) a working memory test modeled after the Auditory Consonant Trigram Test; (3) a phonemic verbal fluency test of executive functioning; (4) a visuomotor coding test of processing speed modeled after the Coding subtest from the Wechsler Adult Intelligence Scales (WAIS; Wechsler, 1997); and (5) a delayed recall trial of the word list. Each subtest was administered the tests and scored according to published guidelines.

Neuroimaging data acquisition and preprocessing

Diffusion weighted images (DWIs) and T1-weighted anatomical MR images were collected from each subject on a research-dedicated 3-T Philips Intera Achieva scanner (Philips Healthcare, The Netherlands). DWIs were acquired using an eight-channel sensitivity encoding (SENSE) head coil with the following parameters: repetition time (TR)=10000 ms, echo time (TE)=48 ms, field of view (FOV)=240×240 mm², B0 image and 92 diffusion directions at B=1000 s/mm², flip angle=90°, matrix size=96×96, voxel size=2.5 mm isotropic, and number of slices=52. The high-resolution T1-weighted anatomical image included

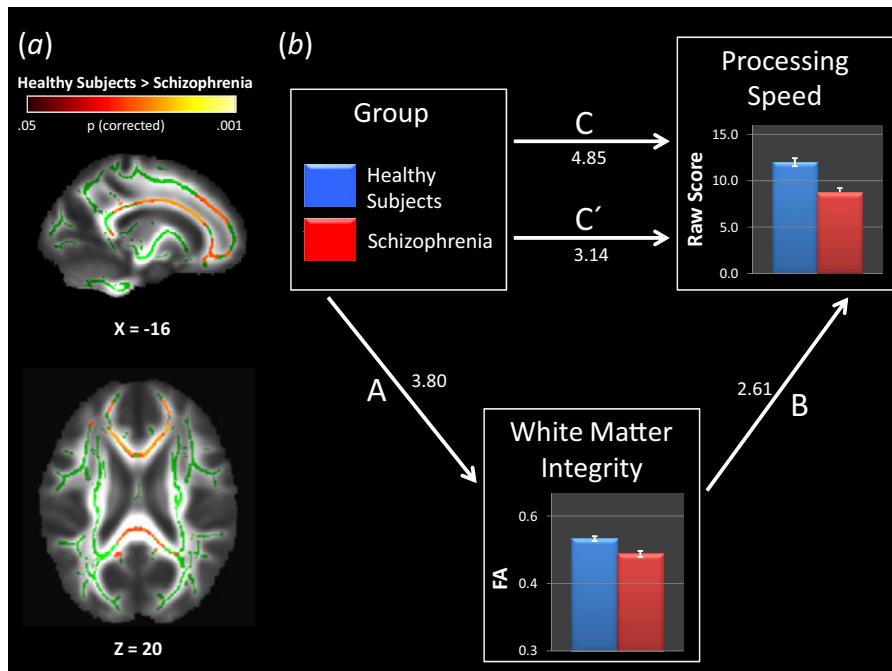


Fig. 1. Reduced white matter (WM) integrity and processing speed impairment in schizophrenia. *(a)* WM integrity, inferred from fractional anisotropy (FA), was reduced in several brain areas in schizophrenia including the corpus callosum, superior frontal gyrus WM and precuneus WM. Areas demonstrating reduced FA in schizophrenia (i.e. warm colors) are overlaid on the skeletonized FA map (i.e. green). *(b)* Processing speed impairment in schizophrenia was partially mediated by mean FA from the regions that demonstrated lower FA in patients compared to healthy subjects. Standardized coefficients, all of which were significant ($p<0.05$), are shown for each pathway. The Sobel test confirmed that the strength of the association between the independent variable (group) and dependent variable (processing speed) was reduced after accounting for WM integrity (path C v. C': $\beta=0.48$, bootstrap confidence interval 0.18–0.92, $p<0.05$).

170 sagittal slices with 1.0-mm isotropic resolution. The DWIs were pre-processed using the Analysis Group at the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL) version 4.1.4 (www.fmrib.ox.ac.uk/fsl/; Behrens *et al.* 2003; Smith *et al.* 2004). Raw DTI data were corrected for eddy current distortions using the Eddy Current Correction (ECC) tool and for motion using the McFlirt Motion Correction tool. The FMRIB Brain Extraction Tool (BET; Smith, 2002) was then used for skull stripping. Diffusion tensors were fitted at each voxel and FA images were created using the DTIFIT tool of FMRIB FDT toolbox, version 2.0 (Behrens *et al.* 2003).

TBSS analysis

Voxel-wise statistical analysis of the DTI FA images was carried out using TBSS (Smith *et al.* 2006) in FSL. First, each subject's FA image was aligned to the standard $1\times 1\times 1$ mm MNI152 template in FSL using the non-linear registration tool (FNIRT). Next, the mean FA image was created and thinned to create a mean FA skeleton representing the centers of all tracts using a threshold of 0.25. Each subject's aligned

FA map was then projected onto this skeleton resulting in each subject's skeletonized FA image.

Statistical analyses

Given our *a priori* interest in understanding the neural correlates of processing speed impairment, a mediation analysis was performed to estimate the direct and indirect relationships between group, WM integrity and processing speed. Parameter estimates were computed for each path in the mediation analysis: A, B, C, C' (see Fig. 1*b*). First, the association between neuropsychological functioning and diagnostic group (i.e. path C) was established by carrying out an independent groups *t* test. Once this was confirmed, we tested to see whether there was a relationship between group and the mediator variable, WM integrity (i.e. path A). Group differences in voxel-wise FA were examined by entering each subject's skeletonized FA into a general linear model (two-sample *t* test) design matrix with non-parametric permutation testing using the randomize tool in FSL (10000 permutations). The results were thresholded at $p=0.05$ (corrected) using the threshold-free cluster enhancement (TFCE) option to find clusters without setting an initial cluster level

(Smith & Nichols, 2009). From this, we extracted the mean FA from all voxels demonstrating a group difference from each subject's skeletonized FA image. Thus, each subject contributed a single value to the mediation analysis that reflected mean FA within the regions identified in the between-groups analysis. Mean FA was then regressed onto processing speed (i.e. path B). Finally, a regression analysis with group and the mediator variable (i.e. mean FA from regions showing between-groups differences) entered as predictors was performed (i.e. path C'). We used the Sobel test to determine the significance of the mediation effect. We also used a bootstrap method (Preacher & Hayes, 2004) to confirm the results of the Sobel test based on evidence that traditional methods have normality assumptions that are rarely met (Hayes, 2009) or suffer from low statistical power (MacKinnon et al. 2002). Bootstrap methods are distribution free and provide greater statistical power. We estimated the 95% confidence interval (CI) of the coefficient from the Sobel test; intervals that did not include zero were considered statistically significant. To determine whether the relationship was most robust for processing speed, we repeated the mediation analysis with the verbal learning, delayed recall, working memory and verbal fluency subtest scores entered as dependent variables.

In addition to determining whether processing speed impairment in schizophrenia was mediated by WM integrity, we also investigated the extent to which abnormal WM integrity in schizophrenia was accounted for by cognitive impairment. That is, we were interested in determining whether WM differences associated with the categorical disease dimension were accounted for by individual differences in the dimension of cognitive impairment. To address this question, we repeated the voxel-wise between-groups analysis of FA entering each of the SCIP domains, processing speed, verbal learning, verbal fluency, working memory and delayed recall, separately as covariates in ANCOVAs. The results from these analyses show group differences on a voxel-wise basis after covarying for impairment in each neuropsychological domain.

Results

Demographics and neuropsychological test scores

Two subjects (one with schizophrenia and one healthy subject) were excluded from the study because of suspected artifacts in the imaging data. Therefore, the final sample consisted of 25 schizophrenia patients and 19 healthy controls. Demographic data for the two groups are presented in Table 1. Level of education

was lower in schizophrenia compared to healthy subjects ($t=3.52$, $p=0.001$). The two groups were otherwise well-matched on age, parental education, sex, race and estimated pre-morbid intellectual functioning. With respect to clinical variables, the average age of onset and duration of illness were approximately 20 and 19 years respectively. Most patients were taking one atypical antipsychotic ($n=15$), with the remaining patients taking two atypical antipsychotics ($n=2$) and one typical antipsychotic ($n=2$). Three patients were unmedicated and medication status could not be determined for three patients. The average antipsychotic dosage among the medicated patients, calculated in chlorpromazine equivalents using the guidelines established by Gardner et al. (2010), was 515.3 ± 216.5 mg/day. Consistent with expectations, schizophrenia patients performed worse on all subtests of the SCIP, except the verbal fluency subtest (see Table 1).

Group differences in WM integrity

Whole-brain voxel-wise analysis revealed decreased FA in several brain regions in schizophrenia, including the genu, body and splenium of the corpus callosum, cingulum, bilateral superior and inferior frontal subgyral WM, bilateral anterior corona radiata and right precuneus WM (see Fig. 1a). There were no significant increases in FA in schizophrenia patients compared to healthy controls.

Relationship between cognitive impairment in schizophrenia and WM integrity

Consistent with our hypothesis, processing speed impairment in schizophrenia was partially mediated by WM integrity (Fig. 1b). Specifically, patients performed worse than healthy subjects on the SCIP processing speed subtest (i.e. path C: $t_{42}=4.85$, $p<0.0001$) and this effect was substantially attenuated when WM integrity was added as an additional predictor (i.e. path C': $t_{42}=3.15$, $p=0.003$). The Sobel test confirmed that the relationship between schizophrenia and processing speed was partially mediated by WM integrity ($\beta=0.48$, bootstrap CI 0.18–0.92, $p<0.05$). Repetition of the mediation analysis with verbal learning, working memory, verbal fluency and delayed recall entered as the dependent variable confirmed that the relationship was strongest for processing speed (see online Supplemental Table 1). Specifically, even though verbal learning, working memory and delayed recall were robustly impaired in schizophrenia, FA did not mediate these relationships (β values ranged from 0.11 to 0.31 and all CIs for the mediation test included zero). To further investigate the selectivity of the relationship between WM and processing speed, we calculated a SCIP composite score by converting raw

Table 1. Demographic characteristics and cognitive tests scores

Variable	Controls		Schizophrenia		χ^2	df	p
	Mean	S.D.	Mean	S.D.	t	df	p
n	19		25				
Gender (male:female)	10:9		13:12		0.00	1	0.967
Ethnicity (White:AA:Other)	9:10:0		13:11:1		0.97	2	0.614
Age (years)	37.4	12.3	39.8	12.8	0.64	42	0.524
Education ^a	6.5	2.0	4.3	2.0	3.52	40	0.001
Parental education ^b	5.0	2.2	4.1	2.2	1.27	39	0.209
Estimated pre-morbid IQ	103.7	13.7	100.8	13.8	0.69	42	0.490
Age of illness onset (years)	–	–	19.9	8.5	–	–	–
Duration of illness (years)	–	–	19.5	11.7	–	–	–
CPZ equivalents (mg/day)	–	–	515.3	216.5	–	–	–
Cognitive test scores							
Verbal learning	23.4	2.6	20.1	3.8	3.25	42	0.002
Working memory	20.2	2.7	17.2	3.7	2.93	42	0.006
Verbal fluency	17.8	3.9	17.1	4.2	0.58	42	0.562
Delayed recall	7.2	1.3	5.9	2.2	2.27	42	0.028
Processing speed	12.0	1.9	8.7	2.4	4.85	42	<0.001

AA, African American; CPZ, chlorpromazine; df, degrees of freedom; s.d., standard deviation.

^aData on education were unavailable for two schizophrenia patients.

^bData on parental education were unavailable for three schizophrenia patients.

subtest scores to Z scores using published normative data and averaging them together, excluding the processing speed measure, and performed a mediation analysis with the SCIP composite score as the dependent variable. As expected, the SCIP composite score was lower in schizophrenia compared to healthy subjects (path C: $t_{42}=3.91$, $p<0.001$, effect size=−1.20). However, the effect was not substantially attenuated when WM integrity was added as a predictor (i.e. path C': $t_{42}=2.98$, $p=0.005$; Sobel test $\beta=0.04$, bootstrap CI −0.13 to −0.19), indicating that impaired overall cognitive ability in schizophrenia was not mediated by WM integrity.

A voxel-wise correlation analysis was performed to further investigate the relationship between processing speed impairment and WM integrity. Specifically, each schizophrenia patient's skeletonized FA map was entered into a general linear model with processing speed test scores entered as a predictor. As with the between-groups analysis, 10 000 iterations of a random permutation method (randomize tool, FSL) and the TFCE option were used to find clusters without setting an initial cluster level. The resultant statistical maps were masked by the between-group differences image, and thresholded at $p<0.05$. This analysis was repeated entering the remaining SCIP subtest scores as a predictor to determine whether other cognitive functions also correlated with FA. As shown in Fig. 2a,

several of the regions that demonstrated reduced FA in schizophrenia also correlated positively with processing speed in the patient group, including the genu and body of corpus callosum, bilateral superior and inferior frontal subgyral WM, and left anterior corona radiata. By contrast, FA did not correlate with verbal learning, working memory, verbal fluency and delayed recall (see Fig. 2b–e).

Group differences in WM integrity after controlling for cognitive impairment

To further examine the impact of cognitive functioning on WM integrity in schizophrenia, the whole-brain analysis of group differences in WM integrity was repeated including each of the SCIP subtests as a covariate in separate ANCOVAs. As shown in Fig. 3, after accounting for processing speed, there were no significant group differences in FA anywhere in the brain, even when a more liberal threshold of $p=0.10$ (corrected) was used. By contrast, significant differences persisted after correcting for working memory and verbal fluency. The group differences were also mitigated to some extent when verbal learning was included as a covariate; however, the same general pattern of reduced WM integrity observed in the no-covariate analysis was apparent at the more liberal threshold of $p=0.10$ (corrected).

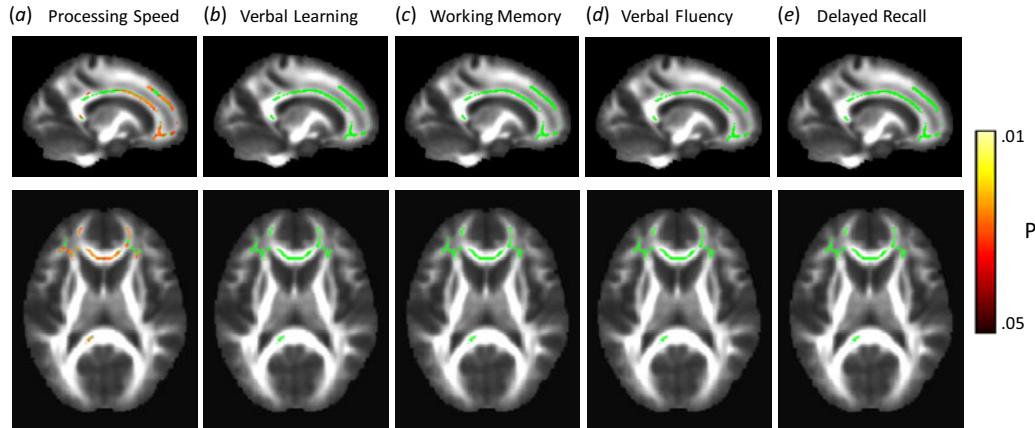


Fig. 2. Correlations between white matter (WM) integrity, inferred from fractional anisotropy (FA), and cognition in schizophrenia. (a) Processing speed correlated with FA in the corpus callosum and superior frontal gyrus. (b–e) WM integrity was not correlated with other cognitive domains.

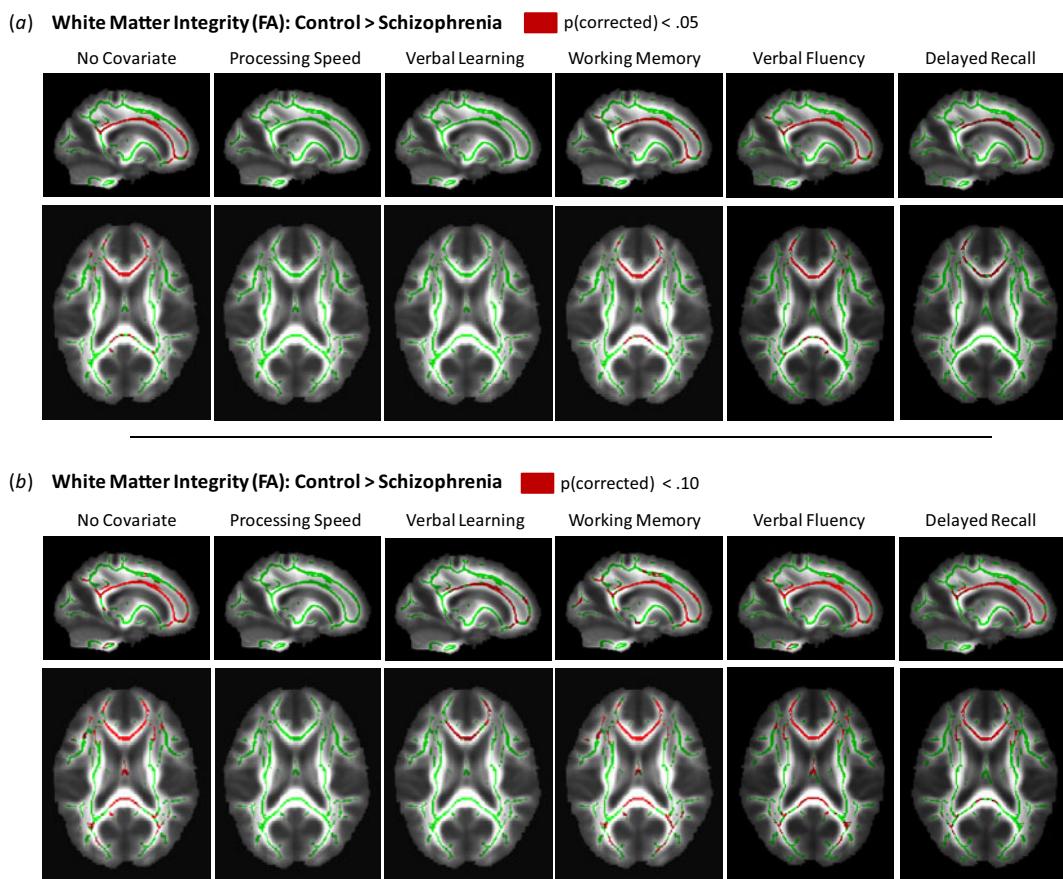


Fig. 3. White matter (WM) integrity reductions in schizophrenia with and without covarying for cognition. Without covarying for cognitive impairment, WM integrity, inferred from fractional anisotropy (FA), was reduced in multiple brain areas in schizophrenia at both (a) conservative ($p<0.05$) and (b) liberal statistical thresholds ($p<0.10$). Similar results were observed after covarying for working memory, verbal fluency, delayed recall and, to a lesser extent, verbal learning. By contrast, no group differences were observed after covarying for processing speed at either the conservative or liberal statistical thresholds. Statistical parametric maps (i.e. warm colors) are overlaid on the skeletonized FA map (i.e. green).

Discussion

Cognitive impairment, and slowed processing speed in particular, is an important predictor of functional outcome in schizophrenia and a potential endophenotype of the disorder (Dickinson *et al.* 2007; Sanchez *et al.* 2009; Nuechterlein *et al.* 2011). Prompted by compelling evidence that brain anatomical connectivity is related to processing speed in healthy subjects, we investigated the relationship between WM integrity and processing speed, and cognitive functioning more broadly, in schizophrenia. We hypothesized that: (1) consistent with prior studies, the integrity of key WM tracts would be reduced in schizophrenia; and (2) cognitive impairment, especially processing speed impairment, would be mediated by WM integrity. Our results support these hypotheses. Specifically, WM integrity in the corpus callosum, frontal lobe, cingulum, anterior corona radiata and precuneus was reduced in schizophrenia. Importantly, processing speed impairment in schizophrenia was partially mediated by WM integrity in these regions. The relationship between cognitive functioning and WM integrity was strongest for processing speed as impairments in other cognitive domains, including working memory, verbal learning and executive functioning, were not mediated by WM integrity. Finally, in an effort to further understand the relationship between cognition and WM integrity in schizophrenia, we examined the extent to which WM reductions associated with the categorical diagnosis of schizophrenia were accounted for by variation in the dimension of cognitive impairment. The results of this analysis revealed that disrupted WM integrity in schizophrenia is largely accounted for by individual differences in processing speed impairment. By contrast, group differences in WM integrity persisted after impairment in other cognitive domains were accounted for, including working memory and executive functioning. Combined, our findings implicate reduced WM integrity in the expression of cognitive impairment in schizophrenia, especially slowed processing speed, and indicate that WM integrity in schizophrenia covaries with individual differences in the severity of processing speed impairment.

Several limitations of our investigation merit discussion before considering the potential implications of our findings. First, the sample sizes, although comparable to most psychiatric neuroimaging investigations, are modest for mediation analysis. For instance, power analysis based on Fritz & MacKinnon (2007) indicates that we were well-powered (i.e. > 80%) to detect large effect sizes for the 'a' and 'b' paths of the mediation model for processing speed. However, for the other cognitive variables, which had smaller effects for the 'b' paths (all Cohen's $d < 0.30$), we would have

needed considerably larger sample sizes to reach 80% power to detect an effect. Thus, although our findings speak to the strength of the relationship between WM integrity and processing speed impairment in schizophrenia, we cannot rule out the possibility that deficits in other cognitive domains are also partially mediated by WM integrity. Indeed, our ANCOVAs revealed that, similar to processing speed, no group differences in WM were detected after covarying for verbal learning at the standard $p=0.05$ (corrected) threshold. However, in contrast to the ANCOVA covarying for processing speed, significant group differences remained at the more liberal threshold of $p=0.10$ (corrected) after covarying for verbal learning. This suggests that verbal learning also accounts for some of the variability in reduced WM integrity in schizophrenia, but less than processing speed. Larger sample sizes will probably be needed to more accurately determine the extent to which specific cognitive domains are related to WM pathology in schizophrenia. A second limitation is that the SCIP, although a very good approximate of overall cognitive functioning, is not a replacement for a comprehensive neuropsychological assessment (Cuesta *et al.* 2011). It is possible that other cognitive domains, in addition to processing speed, might have been linked to WM integrity had we used a more extensive battery. However, the fact that a specific relationship between processing speed and WM was detected with a relatively brief battery is all the more striking as more extensive neuropsychological batteries generally result in greater independence between cognitive domains, not less, and greater power for detecting specific brain-behavior relationships. Additionally, processing speed, as measured with commonly used neuropsychological tests, taps a wide range of cognitive abilities, raising questions about which specific cognitive operations contributing to neuropsychological tests of processing speed are related to WM integrity. Finer-grained measures capable of parsing the specific cognitive operations involved in processing speed will be required to address this limitation. Finally, our decision to focus on overall WM integrity derived from voxels identified in the between-groups analysis might have limited our ability to detect more spatially circumscribed associations between cognition and WM. A voxel-wise approach is more sensitive in this case; however, there is considerable debate in the neuroimaging field about the validity of voxel-wise brain-behavior correlation analyses, with some investigators arguing that exploratory, whole-brain voxel-wise correlation analyses yield inflated estimates of effect size when not tested in an independent data set (e.g. Vul & Pashler, 2012). Thus, although our mediation analysis is methodological sound as it focused on mean FA

extracted from regions identified *a priori* in the between-groups analysis, it might be insensitive to detecting WM–cognition associations that are spatially circumscribed, and the voxel-wise correlation analysis examining the relationship between WM integrity and cognition in schizophrenia should be interpreted cautiously until replicated.

Consistent with many prior studies, we found reductions in WM integrity in schizophrenia that included many tracts often implicated in the disorder, including the corpus callosum, cingulum and anterior corona radiata (Melonakos *et al.* 2011; Fitzsimmons *et al.* 2013). However, the findings across studies are remarkably heterogeneous, with some investigations reporting widespread decreases in WM integrity and others reporting circumscribed reductions or, in the case of a small minority of studies, no changes at all (e.g. Nenadic *et al.* 2011). By linking the severity of WM pathology to individual differences in processing speed impairment, our results provide a potential explanation for the variable findings. The current results also have implications for dimensional approaches to parsing the heterogeneity of schizophrenia (Cuthbert & Insel, 2013). Specifically, the fact that we did not find any effect of schizophrenia diagnosis on WM integrity after covarying for processing speed indicates that the changes in WM associated with the categorical illness variable were accounted for by variability in a specific dimension of the illness. This was not the case for several other cognitive domains prominently affected in schizophrenia, indicating that the association between processing speed and WM integrity was unlikely to be a statistical artifact related to co-linearity (i.e. strong association between processing speed impairment and schizophrenia). In particular, widespread reductions in the integrity of the corpus callosum and prefrontal cortex WM remained after covarying for working memory, executive functions and verbal memory, all of which were impaired in schizophrenia. Our results make a compelling case that WM pathology in schizophrenia is related to cognitive impairment and provide further support for dimensional approaches to dissecting the heterogeneity of schizophrenia.

The association between processing speed impairment and reduced WM integrity in schizophrenia, while correlational in nature, raises the possibility that the two features result from a common etiological mechanism. The high heritability of schizophrenia, along with strong evidence that WM integrity, inferred from FA, and processing speed are also heritable, implicates a genetic basis (Touloupolou *et al.* 2007; Doherty *et al.* 2012; Jahanshad *et al.* 2013). This is supported by evidence that the integrity of WM tracts prominently affected in probands, such as the corpus

callosum, is reduced in unaffected relatives of patients (Knochel *et al.* 2012). Imaging genetic studies have linked allelic variation in several putative schizophrenia risk genes, including *CNTNAP2*, *NTRK1*, *NTRK3* and *MIR137*, to WM integrity (Braskie *et al.* 2012, 2013; Clemm von Hohenberg *et al.* 2013; Lett *et al.* 2013). However, there are also negative findings. For instance, the genome-wide risk gene *ZNF804A* seems to be unrelated to WM integrity (Sprooten *et al.* 2012; Wei *et al.* 2013). Recently, Voineskos *et al.* (2013) found that the effect of several risk alleles in oligodendrocyte genes on cognition, including *MAG*, *CNP* and *OLIG2*, was mediated by WM integrity, thus establishing a putative pathway linking genetic variation within WM genes to WM integrity and, ultimately, cognition.

The current results may also have implications for the prevention and treatment of cognitive impairment in schizophrenia. Both deficient processing speed and reductions in WM integrity are observed in individuals at high risk for psychosis, with those who go on to develop a full-blown psychotic disorder demonstrating worse cognition and more WM pathology than non-converters (Karlsgodt *et al.* 2009; Carletti *et al.* 2012). In patients with schizophrenia, chronic patients demonstrate greater WM changes than first-episode patients (Friedman *et al.* 2008). It is not known whether cognitive decline and changes in anatomical brain connectivity move in parallel during the transition to psychosis, or over the course of the illness. However, interventions designed to preserve the integrity of WM in high-risk populations, or ameliorate WM deterioration in patients, may ward off cognitive impairment and/or reduce deterioration over the course of the illness. Moreover, evidence that processing speed impairment mediates deficits in other cognitive domains suggests that the benefits of improving processing speed could be widespread (Rodriguez-Sanchez *et al.* 2007; Andersen *et al.* 2013). For instance, Anderson *et al.* (2013) found that deficits in other cognitive domains, including working memory, verbal memory and executive function, were mediated by processing speed. Mounting pre-clinical and clinical evidence supporting myelin dysfunction in schizophrenia implies that drugs that improve or preserve myelin might prove effective in the disorder, as some have suggested (Walterfang *et al.* 2011). There is also accumulating evidence that cognitive remediation improves WM integrity. Recently, Penades *et al.* (2013) found that WM integrity of the genu of the corpus callosum, a region that mediated processing speed impairment in the current investigation, increased to a greater extent in patients receiving cognitive remediation compared to a treatment control group. Although Penades *et al.* (2013) found no effect of cognitive remediation on processing speed, a meta-analysis by Wykes *et al.* (2011)

concluded that cognitive remediation does have a modest effect on processing speed. However, it is important to note that processing speed impairment was only partially mediated by WM integrity. Clearly, other factors, including possible gray matter changes and functional abnormalities, also contribute to processing speed dysfunction.

In conclusion, we found that cognitive functioning, particularly processing speed impairment in schizophrenia, is mediated by decreased WM integrity. Moreover, we did not detect any differences in WM integrity between healthy subjects and individuals with schizophrenia after accounting for individual differences in processing speed. Importantly, the relationship between WM and cognitive impairment was most robust for processing speed; deficits in other cognitive domains affected in schizophrenia, including working memory, verbal memory and overall cognitive impairment, were not mediated by WM integrity. However, larger sample sizes will be required to determine the extent to which deficits in other cognitive domains are mediated by WM integrity. The results suggest that a common etiological mechanism, possibly genetic, might underlie processing speed impairment and WM pathology, and further imply that interventions that preserve and/or improve WM integrity may enhance cognition.

Supplementary material

For supplementary material accompanying this paper, please visit <http://dx.doi.org/10.1017/S0033291714001111>.

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Declaration of Interest

None.

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