The COMT Val[158]Met polymorphism moderates the association between cognitive functions and white matter microstructure in schizophrenia

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Objectives Impaired cognitive functioning is a core feature of schizophrenia. Cognitive impairment in schizophrenia has been associated with white-matter (WM) abnormalities and degenerative changes of cortical myelin in the cerebral cortex. Furthermore, findings suggested a role of the *COMT* gene in affecting both WM and neuropsychological performances. We thus hypothesized that the *COMT* Val[158]Met genotype would affect the association between cognitive functions and WM microstructure in a sample of schizophrenic patients.

Materials and methods Seventy-eight schizophrenic patients performed the brief assessment of cognition in schizophrenia for assessment of cognitive performances. Sixty-nine patients provided a venous blood sample for genotypic analysis. WM integrity was evaluated using tract-based spatial statistics with threshold-free cluster enhancement ($P < 0.05$).

Results Analysis indicated an association between cognitive functions and WM microstructure in the Val/Val group, but not in the Met carriers group. WM tracts include the corpus callosum, thalamic radiations, corona radiata, forceps major and minor, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and cingulum.

Conclusion Results suggested a moderating effect of the *COMT* Val[158]Met polymorphism on the association between cognitive functioning and WM microstructure. Our findings support the importance of myelination in cognition, identifying measures of WM microstructure as important neurobiological features of cognitive performances. *Psychiatr Genet* 26:193–202 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

Impairment in cognitive functioning is a core feature of schizophrenia, has been suggested to partially explain psychiatric symptoms (Galletly *et al.*, 2000), and has been identified as an intermediate phenotype for this disorder (Gottesman and Gould, 2003). A stable trait-like dimension of the disorder, neuropsychological impairment appears as chronically disabling and sometimes it arises before the onset of the illness (Heaton *et al.*, 2001). Cognitive functions are associated with functional outcome, interpersonal, occupational, and problem-solving skills (Silverstein *et al.*, 1998; Green *et al.*, 2000).

A single nucleotide polymorphism in the gene coding for catechol-O-methyltransferase (COMT) was consistently included among factors affecting cognitive functioning. The *COMT* gene is located at 22q11.2, a chromosomal region that has been implicated in schizophrenia by linkage (Owen *et al.*, 2004; Stefansson *et al.*, 2008), and encodes a long and a short transcript. The long transcript can be translated into soluble (S) and membrane-bound (MB) forms, the latter modulating cortical dopamine brain signaling (Matsumoto *et al.*, 2003; Meyer-Lindenberg *et al.*, 2005; Papaleo *et al.*, 2008) in the prefrontal cortex because of their abundance and a relative lack of dopamine transporters (Meyer-Lindenberg *et al.*, 2005). A single nucleotide polymorphism at codon 158 in the *COMT* gene, rs4680 (Val[158]Met), results in two allelic variants associated with high (Val) versus low (Met) enzyme activity (Lotta *et al.*, 1995; Lachman *et al.*, 1996). Met homozygotes show one-third less activity than Val ones (Chen *et al.*, 2004) and better cognitive function (Winterer and Goldman, 2003).

Several studies identified an association between the *COMT* genotype and cognitive functions relying on the prefrontal cortex in patients with schizophrenia and their relatives, with homozygotes for the Met allele performing better than Val/Val (Ira *et al.*, 2013). Others found no effects (Szoke *et al.*, 2006; Barnett *et al.*, 2007; Lopez-Garcia *et al.*, 2013), thus suggesting that other factors may interact with *COMT* in affecting cognition.

Cognitive impairment in animal models and in schizophrenia has been associated with white-matter (WM) abnormalities (Dwork *et al.*, 2007) and with degenerative changes of cortical myelin in the cerebral cortex (Peters *et al.*, 2000; Peters and Sethares, 2002). WM microstructure can be investigated *in vivo* by diffusion tensor imaging (DTI). Anisotropy can be estimated through the application of diffusion-sensitizing gradients and the calculation of elements of the diffusion tensor matrix, that is the three eigenvalues λ_1, λ_2, and λ_3 (Taylor *et al.*, 2004). The tendency to diffuse along the principal direction of the fiber [axial diffusivity (AD)] is the principal diffusion eigenvalue (λ_1) and reflects the integrity of axons and myelin sheaths, and the bundle coherence of WM tracts (Boretius *et al.*, 2012). An increase in radial diffusivity (RD, the average of λ_2 and λ_3), perpendicular to axonal walls, suggests disrupted myelination (Song *et al.*, 2002). Mean diffusivity (MD, average of λ_1, λ_2 and λ_3) is a measure of the average molecular motion, independent of tissue directionality. Fractional anisotropy (FA) is the square root of the sum of squares of the diffusivity differences divided by the square root of the sum of squares of the three diffusivities. Changes in FA have been shown to mediate impairment of processing speed (Karbasforoushan *et al.*, 2015), verbal learning, and visual learning (Liu *et al.*, 2013).

Few studies have investigated the effect of the *COMT* polymorphism on WM microstructure. Among healthy children, Met carriers showed reduced FA in the genu of the corpus callosum, anterior thalamic radiation, and uncinate fasciculus, together with increased AD and RD (Thomason *et al.*, 2010). Met carriers also showed larger WM hyperintensities in subcortical regions (Liu *et al.*, 2014) and reduced intelligence-related FA in the corticospinal tract of healthy individuals (Liu *et al.*, 2010). Substance abuser Met/Met homozygotes showed reduced FA in the prefrontal cortex (Zhang *et al.*, 2013) and depressed patients who were Met carriers showed the same reduction in the inferior longitudinal fasciculus, bilateral middle temporal gyrus, right frontal gyrus, and right cingulum bundle area (Seok *et al.*, 2013), and a reduction of AD in the right temporal lobe (Hayashi *et al.*, 2014). Finally, Met carriers showed reduced WM density in the cerebellum in velocardiofacial syndrome (Van Amelsvoort *et al.*, 2008) and reduced WM connectivity in a network linking 18 different brain regions in patients with attention deficit hyperactivity disorder (Hong *et al.*, 2015). A single study in healthy individuals, however, showed higher FA and lower mean diffusivity (MD) in Met/Met patients in the superior longitudinal fasciculus, cingulate gyrus, forceps minor, and inferior fronto-occipital fasciculus, in very old age (81–87 years), with no associations in younger patients (60–78 years) (Papenberg *et al.*, 2015), and other studies found increased FA in posterior thalamic radiation, posterior and superior corona radiata, and superior longitudinal fasciculus in Met carriers with panic disorder (Kim *et al.*, 2013).

Albeit sparse, this evidence suggested the relevance of *COMT* rs4680 and WM microstructure as factors affecting human cognition in health and disease, but did not explore their interaction. We investigated these factors in a homogeneous sample of patients with schizophrenia.

Materials and methods
Participants
Seventy-eight patients (51 men and 27 women) diagnosed with chronic schizophrenia were recruited from the psychiatric ward of San Raffaele Turro Hospital in Milan. Exclusion criteria were as follows: mental retardation, lifetime clinically relevant substance abuse including cannabis, history of major unstable physical illness, and other psychiatric comorbidities. Patients were biologically unrelated, clinically stabilized outpatients who fulfilled the *Diagnostic and Statistical Manual of Mental Disorder*, 4th ed. text revision (DSM-IV-TR) criteria for schizophrenia and were responders to typical and atypical antipsychotics in monotherapy (clozapine $n = 27$, risperidone $n = 15$, aripiprazole $n = 7$, haloperidol $n = 13$, paliperidone $n = 6$, olanzapine $n = 10$). Doses had been stable in the 6 months before enrollment. Sixty-nine patients provided a venous blood sample for genotypic analysis. After a complete description of the study was provided to the patients, a written informed consent was obtained. The local ethical committee approved the study protocol.

Clinical and neuropsychological assessment
The diagnosis of schizophrenia was made by trained psychiatrists using the SCID-I questionnaire, mental retardation was assessed by a trained psychologist through WAIS-R, and the severity of symptoms was rated on the positive and negative syndrome scale (Kay *et al.*, 1987).

Cognitive functions were assessed by the brief assessment of cognition in schizophrenia (Keefe *et al.*, 2004), a broad battery evaluating several domains of cognition (verbal memory, working memory, psychomotor speed and coordination, attention and speed of information processing, verbal fluency, and executive functions).

Polymorphisms' identification
DNA was extracted from whole blood by manual extraction using the 'Illustra blood genomicPrep Midi Flow kit' (GE Healthcare, Milan, Italy). PCR was performed with the following primers: 5′-ACT GTG GCT ACT CAG CTG TG-3′, 5′-CCT TTT TCC AGG TCT GAC AA-3′. The PCR reaction was carried out using an ABI 9700 PCR thermal-cycler (Applied Biosystems; Applera, Norwalk, Connecticut, USA) in a 10 µl volume containing 150 ng of genomic DNA, 5 pmol of each primer, 10 nmol of dNTPs' mix, 10× HotMaster Taq Buffer, and 0.5 U of HotMaster Taq DNA Polymerase (Eppendorf, Milan, Italy). The amplified fragment was then purified by Multi-Screen Colum Loader (Millipore,

Billerica, Massachusetts, USA), filled up, and packaged with Sephadex G-50 (Sigma-Aldrich's, St Louis, Missouri, USA) to remove residual PCR reagents. An aliquot of a purified PCR product was then used to perform a sequencing reaction using the DYEnamic ET Dye Terminator Cycle Sequencing Kit (GE Healthcare). Then, the sequencing reaction product was purified following the above-mentioned protocol to remove excess fluorescent dyes not incorporated into the DNA fragment. The fragment was then sequenced using a MegaBACE 500 genetic analyzer (GE Healthcare) under standard conditions.

MRI acquisition

All patients underwent volumetric T1 and T2 examinations to exclude the presence of brain lesions and then Diffusion Tensor images were acquired. All the MRI examinations were performed at C.E.R.M.A.C. (Centro di Eccellenza Risonanza Magnetica ad Alto Campo, University Vita-Salute San Raffaele, Milan, Italy) using a 3.0 T MR scanner (Gyroscan Intera; Philips, Best, the Netherlands). Diffusion tensor images were acquired with spin-echo echo-planar imaging and the following parameters: repetition time/echo time = 8753.89/58 ms; 55 contiguous, 2.3 mm thick axial slices with field of view (FOV) = 240 mm; matrix scan 112; reconstructed matrix 128×128; acquired voxel measure, phase and size (mm) = 2.14/2.71/2.30; and reconstructed voxel measure, phase, and size (mm) = 1.88/1.87/2.30, sensitivity encoding acceleration factor = 235 noncollinear directions of the diffusion gradients, b value = 900 s/mm^2. Fat saturation was performed to avoid chemical shift artifacts.

T1 and T2 images were acquired using the same magnet 22 turbo spin echo (Philips). T2 axial slices had repetition time = 3000 ms; echo time = 85 ms; flip angle = 90°; turbo factor 15; and 5 mm-thick, axial slices with a 512×512 matrix and a 230 mm FOV. The T1-weighted sequence had TR 2500 ms, TE 4.6 ms, yielding 220 transversal slices with a thickness of 1.6 mm, 256×256 matrix, and 230 mm of FOV.

Data processing and analyses

Image analyses and tensor calculations were carried out using the 'Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library' (FSL 5.0; *http://www.fmrib.ox.ac.uk/fsl/index.html*) (Smith *et al.*, 2004; Woolrich *et al.*, 2009) (for a detailed description of data processing, see Supplementary Materials, Supplemental digital content 1, *http://links.lww.com/PG/A153*).

Voxelwise DTI analyses were carried out using nonparametric permutation-based testing (Nichols and Holmes, 2002) as implemented in randomise in FSL: we included all patients and (i) we separately tested for linear effects of cognitive functions across genotype and of the *COMT* Val158Met polymorphism on FA, MD, AD, and RD in separate TBSS models; (ii) we tested whether the *COMT* polymorphism moderated the association between cognitive functions and WM integrity by separately testing cognitive functions and WM in the two genotype groups in a single TBSS model. We accounted for the effects of nuisance covariates that could influence WM structure: age (Kochunov *et al.*, 2007), sex (Herting *et al.*, 2012), age at onset of illness, and medication load. Medication load was assessed as the mean chlorpromazine equivalent dose. We converted all antipsychotic doses into chlorpromazine equivalents using published equivalencies for oral conventional (American Psychiatric Association, 1997) and atypical (Woods, 2003) antipsychotics. For depot haloperidol, fluphenazine, and risperidone, we used the manufacturers' recommended equivalent for the depot to oral conversion for the same drug and then converted these into oral chlorpromazine equivalents. Threshold-free cluster enhancement (Smith and Nichols, 2009) was used to avoid defining arbitrary cluster-forming thresholds and smoothing levels. Voxelwise levels of significance, corrected for multiple comparisons, were then calculated with a standard permutation testing by building up the null distribution (across permutation of the input data) of the maximum (across voxels) threshold-free cluster enhancement scores, and then using the 95th percentile of the null distribution, generated by 5000 permutations for each contrast, to threshold signals at corrected P less than 0.05 in a minimum cluster size of $k = 100$.

For genetic analysis, as in previous studies (Bosia *et al.*, 2007, 2014), patients were divided into two groups: those homozygous for the Val allele versus carriers of, at least, one Met allele as previous studies showed no significant differences in cognitive performances between Met homozygous and Val/Met patients (Rosa *et al.*, 2004).

Results

The distribution of genotypes respected the Hardy–Weinberg equilibrium ($\chi^2 = 0.055$, $P = 0.81$) and was the following: Val/Val 21/69 (30.4%), Val/Met 35/69 (50.7%), and Met/Met 13/69 (18.8%). Allelic frequencies were Val 55.8% and Met 44.2%.

The clinical, demographic, and neuropsychological characteristics of the sample are presented in Table 1. No significant differences were found for clinical-demographic variables between the two genotypic groups. For neuropsychological variables, only verbal memory differed significantly between the two groups, with Val/Val homozygotes showing a significantly poorer performance compared with Met-carriers (Table 1).

Cognitive functions associated with WM microstructure in Val/Val homozygotes

Cognitive functions associated with DTI measures of WM microstructure in the group of Val/Val homozygotes and not in Met-carriers. Among Val/Val, each cognitive performance showed positive relationships with AD and

Table 1 Clinical, demographic, and neuropsychological characteristics of the sample as a whole and divided according to the COMT Val[158]Met polymorphism

	Mean ± SD				
	All sample ($N = 78$)	Val/Val ($N = 21$)	Met carriers ($N = 48$)	T/χ	P
Age	37.46 ± 9.19	35.71 ± 7.94	37.98 ± 9.57	0.95	0.346
Age at onset	24.49 ± 5.84	24.57 ± 5.78	24.54 ± 6.1	−0.02	0.985
Education	12.32 ± 3.22	11.95 ± 3.43	12.33 ± 3.04	0.46	0.647
Sex	46 M, 23 F	16 M, 5 F	30 M, 18 F	1.23	0.267
Medical load	328.87 ± 194.37	317.43 ± 186.33	348.34 ± 192.29	0.62	0.537
PANSS positive	18.12 ± 5.26	19.86 ± 5.94	16.63 ± 5.57	−2.23	0.68
PANSS negative	20.8 ± 4.69	20.95 ± 4.79	20.8 ± 5.1	−0.12	0.78
PANSS general	39.27 ± 8.32	38.4 ± 7.82	37.98 ± 9.6	−0.17	0.32
Working memory	16.09 ± 4.56	15.76 ± 4.86	16.67 ± 4.12	0.79	0.429
Verbal fluency	34.12 ± 11.59	34.38 ± 10.44	35.44 ± 12.11	0.35	0.729
Verbal memory	41.88 ± 13.11	38.38 ± 12.25	45.73 ± 11.60	2.38	0.020
Executive functions	13.19 ± 4.57	12.29 ± 5.08	13.52 ± 4.42	1.02	0.311
Attention and speed of information processing	36.74 ± 11.3	34.14 ± 8.59	39.19 ± 11.80	1.76	0.082
Psychomotor coordination	62.96 ± 19.18	67.05 ± 14.14	62.17 ± 21.36	−0.96	0.342

PANSS, positive and negative syndrome scale.

MD, and some functions showed a positive association with RD and a negative association with FA (Table 2 and Fig. 1).

In detail, attention and speed of information processing showed a negative correlation with FA in five clusters with signal peaks in bilateral superior longitudinal fasciculus, the left superior corona radiata, and body of corpus callosum. A positive correlation was observed with AD in two clusters with signal peaks in the bilateral superior longitudinal fasciculus and with RD in two clusters with signal peaks in the right superior longitudinal fasciculus and left superior corona radiata. Finally, a positive association with MD was observed in three clusters with signal peaks in the right superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and external capsule (Supplementary Table S1 and Figs S1, S2, S3 and S4, Supplemental digital content 1, *http://links.lww.com/PG/A153*).

Executive functions showed a positive correlation with AD in two clusters with signal peaks in the right superior longitudinal fasciculus and body of corpus callosum, with RD in two clusters with signal peaks in the left superior longitudinal fasciculus and the right superior corona radiata and with MD with signal peaks in the bilateral anterior thalamic radiation (Supplementary Table S2 and Figs S5, S6 and S7, Supplemental digital content 1, *http://links.lww.com/PG/A153*).

Working memory showed a negative correlation with FA and a positive correlation with AD, RD, and MD (Supplementary Table S3 and Figs S8, S9, S10 and S11, Supplemental digital content 1, *http://links.lww.com/PG/A153*). Three clusters of significance were observed for FA with signal peaks in the left anterior corona radiata and the left superior longitudinal fasciculus. One cluster of significance was observed for AD, showing a signal peak in the right superior longitudinal fasciculus, one cluster of significance was observed for RD showing a

signal peak in the bilateral superior longitudinal fasciculus, and one cluster of significance was observed for MD, showing a signal peak in the right superior longitudinal fasciculus.

Cognitive functions associate with WM microstructure
Considering the entire sample across genotypes, positive relationships were observed between AD, RD, and MD and executive functions (Fig. 2b and Table 3B) and working memory (Fig. 2c and Table 3C), and between AD and MD and attention and speed of information processing in several WM tracts (Fig. 2a and Table 3A). No effect on FA was observed. Affected WM tracts are detailed in Supplementary Materials, Supplemental digital content 1, *http://links.lww.com/PG/A153*.

The COMT Val[158]Met genotype influences WM microstructure
Irrespective of the relationship between WM and cognitive functions, Met carriers showed increased AD compared with Val/Val in four main WM clusters, showing signal peaks in the superior longitudinal fasciculus and anterior thalamic radiation, encompassing the corpus callosum, forceps major, inferior longitudinal fasciculus, cingulum, and inferior fronto-occipital fasciculus (Supplementary Table S7 and Fig. S20, Supplemental digital content 1, *http://links.lww.com/PG/A153*).

Discussion
The *COMT* Val[158]Met polymorphism influenced the relationship between cognitive functions and WM microstructure. In the entire group of patients with schizophrenia, a better performance in working memory, executive functions, and attention and speed of information processing was associated with higher AD, RD, and MD in WM fiber tracts involving interhemispheric and limbic, frontal, parietal, and fronto-occipital connections. This effect was driven by the association, observed in rs4680 Val/Val homozygotes only, of better neuropsychological performance with reduced FA

Table 2 Correlation of cognitive functions scores with DTI measures in Val/Val patients

|	N Voxels and signal peaks (x, y, z)	White matter tracts
(A) Attention and speed of information processing		
Fractional anisotropy		
	1890 29, −59, 25	Right superior longitudinal fasciculus
	988 −24, −4, 34	Left superior corona radiata
0.469±0.083	608 38, −13, 28	Right superior longitudinal fasciculus
	285 −37, −13, 30	Left superior longitudinal fasciculus
	224 −15, −22, 31	Body of corpus callosum
Axial diffusivity		
	6565 −40, −22, 30	Left superior longitudinal fasciculus
1.208±0.198	5848 46, −7, 25	Right superior longitudinal fasciculus
Radial diffusivity		
	5930 28, −58, 25	Right superior longitudinal fasciculus
0.543±0.066	4803 −24, −4, 34	Left superior corona radiata
Mean diffusivity		
	19 950 50, −8, 23	Right superior longitudinal fasciculus
0.756±0.045	463 35, 33, −4	Right inferior fronto-occipital fasciculus
	248 26, 16, −8	Right external capsule
(B) Executive functions		
Axial diffusivity		
	14 906 38, 2, 24	Right superior longitudinal fasciculus
1.186±0.170	14 769 −10, 11, 25	Body of corpus callosum
Radial diffusivity		
	4488 −32, 7, 25	Left superior longitudinal fasciculus
0.546±0.051	3988 26, 2, 34	Right superior corona radiata
Mean diffusivity		
0.748±0.040	18 710 −40, 19, 17	Bilateral anterior thalamic radiation
(C) Working memory		
Fractional anisotropy		
	5075 −18, 22, 26	Left anterior corona radiata
0.452±0.083	363 −43, −40, 33	Left superior longitudinal fasciculus
	247 −46, −45, 24	Left superior longitudinal fasciculus
Axial diffusivity		
1.197±0.203	20 751 49, −15, 28	Right superior longitudinal fasciculus
Radial diffusivity		
0.552±0.058	7784 −24, 14, 31	Left superior longitudinal fasciculus
Mean diffusivity		
	7256 42, 1, 23	Right superior longitudinal fasciculus
0.755±0.047	208 60 46, −3, 25	Right superior longitudinal fasciculus

In the first column, values of the DTI measures of FA, AD, RD, and MD (mean±SD) are presented for regions showing maximal effects on TBSS values (signal peaks). The second column shows dimensions of clusters (number of voxels, mm³) and localization of signal peaks (MNI coordinates). The third column lists the WM tracts significantly associated with cognitive functions in signal peaks.
AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity, MD, mean diffusivity; MNI, Montreal Neurological Institute; WM, white-matter.

and increased AD, RD, and MD. In the Met carrier group, we observed no association of cognitive performance with WM microstructure. In agreement with previous findings (Tsuchimine *et al.*, 2013), rs4680 did not influence the brief assessment of cognition in schizophrenia of cognitive functions independent of WM structure.

The WM tracts involved are crucial to the functional integrity of the brain and have been shown to be affected by schizophrenia (Ardekani *et al.*, 2003; Mcintosh *et al.*, 2008; Rowland *et al.*, 2009; Sussmann *et al.*, 2009; Guo *et al.*, 2012): the left hemisphere (Ashtari *et al.*, 2007; O'Daly *et al.*, 2007), the left superior temporal gyrus (Honea *et al.*, 2005), corpus callosum (Foong *et al.*, 2000; Walterfang *et al.*, 2008), corona radiate (Cheung *et al.*, 2008), insula and anterior thalamic radiation (Bora *et al.*, 2011), and cingulum (Sexton *et al.*, 2010). Reduced FA in schizophrenia is often attributed to greater degrees of RD, suggesting a disturbed or disintegrated myelination, whereas AD is unchanged (Seal *et al.*, 2008; Scheel *et al.*, 2013). However, higher FA was also observed in dopaminergic tracts in the mesencephalon of drug-naive schizophrenics and of their unaffected relatives (Alba-Ferrara and de Erausquin, 2013), and preserved or even increased FA has been associated with duration of untreated psychosis (Filippi *et al.*, 2014) and, in the language and auditory networks, with auditory hallucinations (Hubl *et al.*, 2004; Seok *et al.*, 2007; Rotarska-Jagiela *et al.*, 2009; Mulert *et al.*, 2012; Benetti *et al.*, 2015). Conversely, increased RD has been associated with the effect of antipsychotic agents (Bollettini *et al.*, 2015), thus possibly counterbalancing the detrimental structural high integrity of pathways associated with psychopathology.

A word of caution is needed in the interpretation of the single eigenvalues that lead to AD and RD measures. FA increases with the directional selectivity of water motion, thus reflecting the structure of axonal cell membranes and myelin sheaths, but also the bundle coherence within the WM tracts. Several factors affecting local diffusivity, such as bundle coherence, crossing fibers, or water concentration, can influence FA measures (Pierpaoli *et al.*, 2001; Rose *et al.*, 2008; Chao *et al.*, 2009). In voxels characterized by crossing fibers, AD and RD can show erratic changes, possibly hampering inferences on the underlying tissue structure (Wheeler-Kingshott and Cercignani, 2009). The DTI correlates of acute and chronic demyelination and axon damage may change during the temporal progression of the lesions (Xie *et al.*, 2010). Nevertheless, following the current perspectives, both myelin and axonal microstructure, including microtubules and neurofilaments (Kinoshita *et al.*, 1999), contribute toward AD, which has been associated with fiber diameter or organization (Takahashi *et al.*, 2000). Animal models associated a reduction of AD with axonal injury (Song *et al.*, 2003; Sun *et al.*, 2006) and conversely associated an increase in RD with unchanged AD with dysmyelination (Song *et al.*, 2002). AD and RD might then depend on independent processes (coherence and directionality of axonal structure,
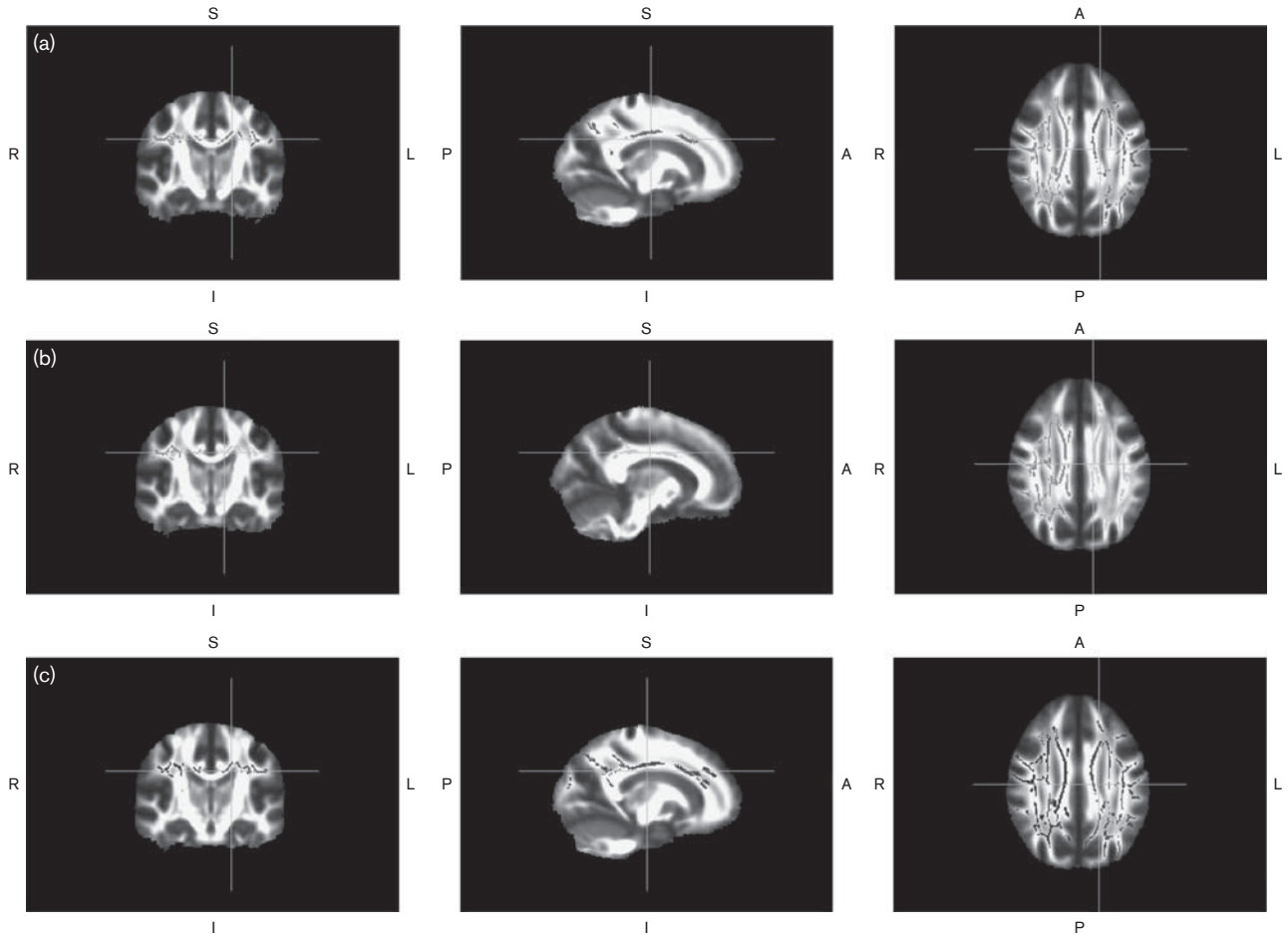
Fig. 1
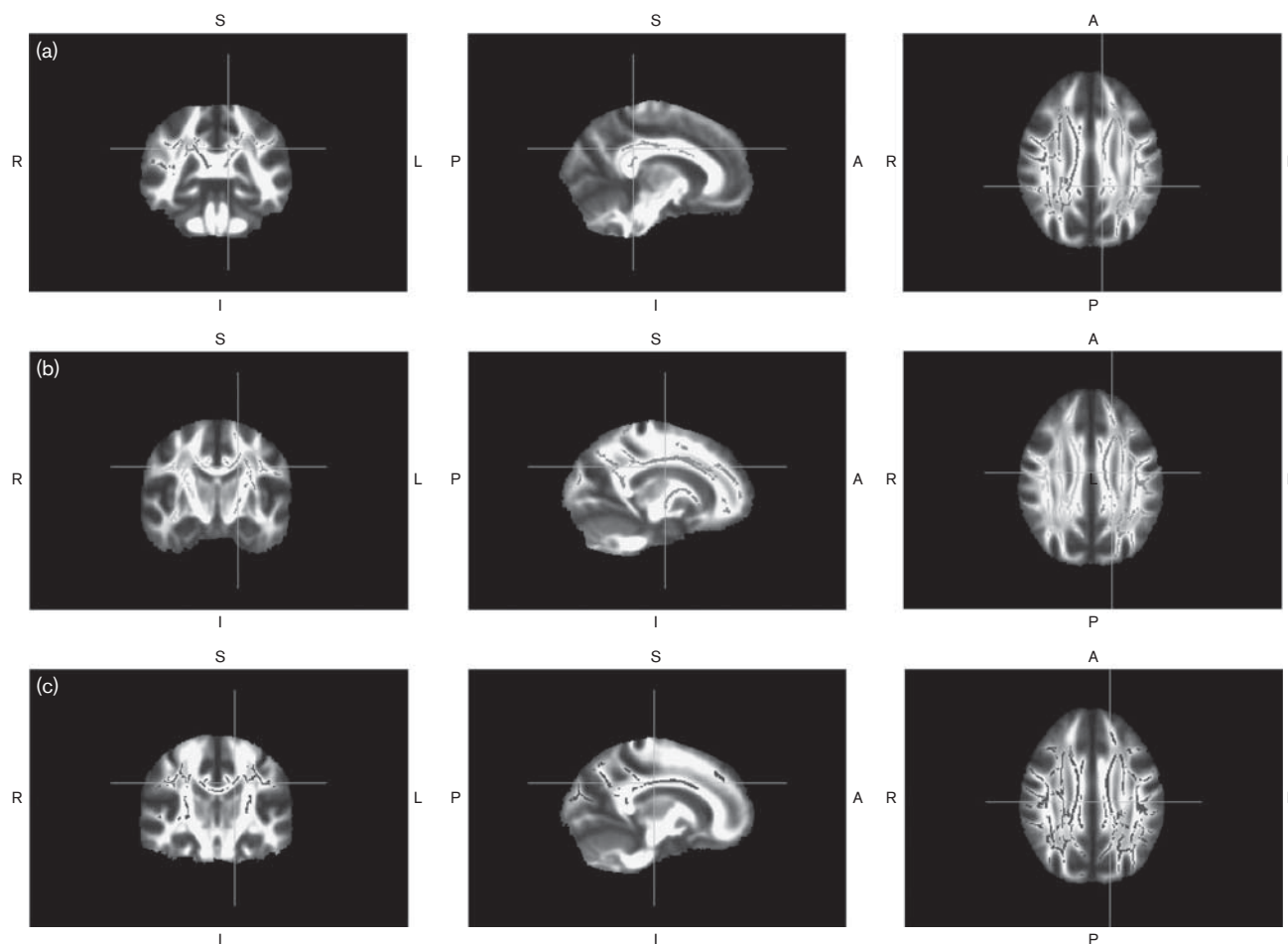
WM areas where a significant association was observed between axial diffusivity and attention and speed of information processing (a), executive functions (b), and working memory (c) in Val/Val patients. Voxels of significant negative correlation are mapped on the mean FA template of the sample studied. The color bar shows $1-P$ values for the observed differences. Numbers show z coordinates in the standard Montreal Neurological Institute (MNI) space. FA, fractional anisotropy; WM, white-matter.

and fiber myelination), the changes of which should not be a priori interpreted as detrimental in schizophrenia. Considering the present findings, better cognitive functions could be associated with increased structural integrity and directionality of axons, including their intracellular microtubular structure, (higher AD), and changes in myelination, possibly including remodeling of myelin sheaths and remyelination (increased RD and lower FA). An increased myelin repair/remyelination could indeed be expected to reduce the thickness of myelin and increase intra-axonal space, and thus increase both RD and AD as observed in the present study. These findings contradict the excessively simplistic postulate that more FA is always better in schizophrenia (Alba-Ferrara and de Erausquin, 2013) and are in agreement with the reported association of higher FA with schizophrenic psychopathology (Hubl *et al.*, 2004; Seok *et al.*, 2007; Rotarska-Jagiela *et al.*, 2009; Mulert *et al.*, 2012; Alba-Ferrara and de Erausquin, 2013; Filippi

et al., 2013; Benetti *et al.*, 2014). Higher FA could be because of a number of pathological factors that may cause higher directionality such as increases in myelination, or microscopic deficits of axonal structures, or decreases in axonal diameter, packing density, and fiber branching, as observed in neurological conditions (Hoeft *et al.*, 2007).

A possible explanation for the influence of *COMT* on WM microstructure arises from the effects of brain catecholamines on the biological process of myelination. In-vitro studies suggest that COMT is synthesized by cultured astrocytes, oligodendrocytes, and neurons (Karhunen *et al.*, 1995; Chen *et al.*, 2011). Dopamine receptor activation has been suggested to directly affect myelination (Bongarzone *et al.*, 1998; Rosin *et al.*, 2005). A direct relationship between dopamine action and myelination has been shown in glial cell culture where D3 receptors

Fig. 2

WM areas where a significant association was observed between axial diffusivity and attention and speed of information processing (a), executive functions (b), and working memory (c) in the entire sample across genotype. Voxels of significant negative correlation are mapped on the mean FA template of the sample studied. The color bar shows $1 - P$ values for the observed differences. Numbers show *z* coordinates in the standard Montreal Neurological Institute (MNI) space. FA, fractional anisotropy; WM, white-matter.

are expressed in immature oligodendrocytes before the peak of myelination, whereas mature oligodendrocytes express D2 receptors (Lindholm and Jazin, 2007). Dopamine signaling pathways genes are poorly expressed in the WM of the human brain (Hawrylycz *et al.*, 2012), but in postmortem brain tissue, mRNA levels of DRD2 were associated significantly with gliogenesis, oligodendrocyte development, and positive regulation of myelination and axon ensheathment, with α-2 adrenergic receptor activity also associating with myelination and ensheathment of neurons (Kim *et al.*, 2012). Considering that the basal transcriptional activity of Met homozygotes is one-third less than Val ones (Chen *et al.*, 2004), differences in cathecolaminergic signaling to oligodendrocytes could result in different behavior of these cells. This mechanism, which requires sound basic studies to be confirmed, could explain the differences between the rs4680 genotype observed in our study.

Altogether, these findings support the interest for DTI measures of WM microstructure as individual biomarkers in patients with schizophrenia, in agreement with neurodevelopment and neurodegenerative models of schizophrenia placing WM at the center stage (Bartzokis, 2002; Kochunov and Hong, 2014). Future studies are needed to investigate how fiber integrity changes during the course of illness and whether specific treatments for cognitive deficits (Poletti *et al.*, 2010) can affect these changes.

The limitations of the study include issues such as generalizability, population stratification, and the lack of a control group. Moreover, the use and reporting of medications varied between patients and it was very difficult to control for the potentially negative effect of medication on neurocognitive function. The drug treatments administered during the course of the illness could have also influenced DTI measures. Future studies should aim at differentiating medication from illness-induced

Table 3 Correlation of cognitive functions scores with DTI measures across genotype

	N Voxels and signal peaks (x, y, z)	White matter tracts
(A) Attention and speed of information processing		
Axial diffusivity		
	2989 20, −27, 50	Right corticol spinal tract
1.21 ± 0.15	1750 48, −37, 16	Right superior longitudinal fasciculus
	301 −22, −23, 37	Left corticospinal tract
Mean diffusivity		
	4966 28, −8, 21	Right superior corona radiata
0.769 ± 0.041	1181 −21, −29, 41	Left superior corona radiata
(B) Executive functions		
Axial diffusivity		
	15 915 28, 5, 28	Right superior corona radiata
1.187 ± 0.17	9256 −10, −10, 29	Body of corpus callosum
	152 −23, −81, 3	Left inferior fronto-occipital fasciculus
Radial diffusivity		
	9247 −27, −4, 28	Left superior corona radiata
0.528 ± 0.072	8633 27, −2, 28	Right superior corona radiata
Mean diffusivity		
0.753 ± 0.44	32 091 27, 5, 27	Left superior corona radiata
(C) Working memory		
Axial diffusivity		
	10 023 20, −37, 31	Right splenium of corpus callosum
1.203 ± 0.171	5893 −47, −16, 28	Left superior longitudinal fasciculus
Radial diffusivity		
	3393 26, 0, 32	Right superior corona radiata
0.556 ± 0.056	148 −25, 14, 31	Left anterior corona radiata
Mean diffusivity		
	7832 26, −35, 26	Right superior longitudinal fasciculus
0.758 ± 0.041	5165 −13, −8, 31	Left body of corpus callosum

In the first column, values of the DTI measures of AD and MD (mean ± SD) are presented for regions showing maximal effects on TBSS values (signal peaks). The second column shows dimensions of clusters (number of voxels, mm³) and localization of signal peaks (MNI coordinates). The third column lists the WM tracts significantly associated to cognitive functions at signal peaks.
AD, axial diffusivity; DTI, diffusion tensor imaging; MD, mean diffusivity; MNI, Montreal Neurological Institute; WM, white-matter.

cognitive dysfunction, which will require a comprehensive assessment with an examination of the cognitive domains mostly affected by specific medications.

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Conflicts of interest

There are no conflicts of interest.

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