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Discoidin domain receptor 1 gene variants are associated with decreased white matter fractional anisotropy and decreased processing speed in schizophrenia

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ABSTRACT

DDR1 has been linked to schizophrenia (SZ) and myelination. Here, we tested whether *DDR1* variants in people at risk for SZ influence white matter (WM) structural variations and cognitive processing speed (PS). First, following a case-control design (*Study 1*), SZ patients (N = 1193) and controls (N = 1839) were genotyped for rs1264323 and rs2267641 at *DDR1*, and the frequencies were compared. We replicated the association between *DDR1* and SZ (rs1264323, adjusted P = 0.015). Carriers of the rs1264323AA combined with the rs2267641AC or CC genotype are at risk to develop SZ compared to the other genotype combinations. Second, SZ patients (*Study 2*, N = 194) underwent an evaluation of PS using the Trail Making Test (TMT) and *DDR1* genotyping. To compare PS between *DDR1* genotype groups, we conducted an analysis of covariance (including rs1264323 as a covariate) and found that SZ patients with the rs2267641CC genotype had decreased PS compared to patients with the AA and AC genotypes. Third, 54 patients (*Study 3*) from Study 2 were selected based on rs1264323 genotype to undergo reevaluation, including a DTI-MRI brain scan. To test for associations between PS, WM microstructure and *DDR1* genotype, we first localized those WM regions where fractional anisotropy (FA) was correlated with PS and tested whether FA showed differences between the rs1264323 genotypes. SZ patients with the rs1264323AA genotype showed decreased FA in WM regions associated with decreased PS. We

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conclude that *DDR1* variants may confer a risk of SZ through WM microstructural alterations leading to cognitive dysfunction.

1. Introduction

Traditionally, schizophrenia (SZ) was thought to be associated with neuronal dysfunction; however, the current hypothesis that myelin and, specifically, oligodendrocytes are also involved in the development of SZ is gaining traction (Ren et al., 2013; Roussos and Haroutunian, 2014). In this regard, after screening the discoidin domain receptor 1 (*DDR1*) locus in DNA from 100 patients diagnosed with SZ, we identified an association of several genetic variants with the disease (Roig et al., 2007). The haplotype encompassing rs1049623, rs2267641 and rs2239518 was associated with SZ after adjusting for multiple testing (Roig et al., 2007).

DDR1 is a membrane-anchored tyrosine kinase receptor whose unique ligand identified to date is collagen (Leitinger, 2014; Ullrich and Schlessinger, 1990; Vogel, 1999). The *DDR1* gene is located at 6p21.3, near the major histocompatibility complex (MHC) region. This chromosomal region has been associated with SZ (Ripke et al., 2013) but most GWAS arrays used in SZ studies did not contain rare variants at the DDR1 locus such as rs2267641. Alternative splicing of *DDR1* produces at least 5 isoforms, known as *DDR1*a to *DDR1*e (Alves et al., 2001). Isoforms *DDR1*a and *DDR1*b are the most abundant in several tissues, including blood (Leitinger, 2014). Detailed analysis of DDR1 protein in the adult human brain revealed that its expression pattern parallels that of the MBP, a classic white matter (WM) protein (Bàrbara Roig et al., 2010). DDR1c isoform expression is highly correlated with the myelin genes *MAG* and *OLIG2* in the human brain (Barbar Roig et al., 2012b). In rodents, high oligodendrocyte expression of *DDR1* parallels developmental myelination (Franco-Pons et al., 2006) and remyelination after experimental demyelination (Franco-Pons et al., 2009). SNP rs2267641, located in a heterogeneous nuclear ribonucleoprotein A2 response element (A2RE) sequence in *DDR1* exon 14, influences alternative splicing and the concentrations of the isoforms *DDR1*b and *DDR1*c (Barbara Roig et al., 2012b). In the same study, SNP rs1264323, which is in linkage disequilibrium (LD) with rs1049623, was also found to influence the expression of isoforms *DDR1*b and *DDR1*c (Barbara Roig et al., 2012b). Moreover, the abundance of the *DDR1c* isoform was significantly elevated in brain dorsolateral prefrontal cortex (DLPFC) tissue from patients with SZ compared to controls (Bàrbara Roig et al., 2012a).

Diffusion tensor imaging (DTI) has made it possible to investigate microstructural WM abnormalities in vivo (Garin-Muga and Borro, 2014). On the basis of DTI data, several studies reported abnormal WM microstructure in patients with chronic and first-episode psychosis (Andreasen et al., 2011; Bora et al., 2011; Pomarol-Clotet et al., 2010; Tamnes and Agartz, 2016) and even in those who were naïve to antipsychotic drugs (Alvarado-Alanis et al., 2015; Zeng et al., 2016; Zhang et al., 2016). Differential expression levels of myelin-related genes, such as *NRG1*, *ERBB4*, *DISC1*, *RTN4R*, *OLIG2*, *CNP* and *MAG*, in brain tissue from subjects with SZ also revealed molecular WM abnormalities, matching the results found by DTI (Roussos and Haroutunian, 2014; Takahashi et al., 2011; Voineskos, 2015). The abnormal expression of myelin-related genes in SZ was most pronounced in the DLPFC, hippocampus, superior temporal cortex and cingulate gyrus (Höistad et al., 2009; Katsel et al., 2005). Only a few reports have demonstrated a relationship among gene variants, WM tract integrity, and cognitive performance. For instance, genetic variability at *MAG*, *OLIG2,* and *CNP* influenced cognitive performance in a manner mediated by the integrity of WM fiber tracts in patients with SZ (Voineskos et al., 2013); more recently, Poletti et al. showed the influence of the *COMT* Val^{158}Met polymorphism on the association between cognitive function and WM microstructure (Poletti et al., 2016). Our present hypothesis is that SNP variants in the *DDR1* locus confer susceptibility to SZ in association with WM microstructure variation and neurocognitive deficits such as processing speed (PS) (Karbasforoushan et al., 2015). To test this hypothesis, we designed 3 different but interrelated studies to achieve three main aims: in Study 1, we aimed to replicate the association between *DDR1* variants and SZ; in Study 2, we aimed to determine whether these *DDR1* variants influence PS; and in Study 3, we assessed whether there is a link between WM microstructure, PS and *DDR1* genotype.

Table 1
Sociodemographic, clinical and neuropsychological characteristics of study participants.

	Study 1 (case-control)		Study 2 (neurocognition)	Study 3 (neuroimaging)
	Control N = 1839	Schizophrenia N = 1193	Schizophrenia N = 194	Schizophrenia N = 54
Sex (% men/% women)	62.2/37.8	71.4/28.6	66.5/33.5	53.7/46.3
Age (mean ± SD for men/women)	51.4 ± 10.0/52.6 ± 9.9	47.4 ± 13.0/53.7 ± 15.0	34.0 ± 9.7/38.0 ± 11.1	32.6 ± 6.8/36.0 ± 9.0
Years of education (mean ± SD)	na	na	10.6 ± 3.1	9.9 ± 2.5
Duration of illness (years, mean ± SD)	na	na	10.1 ± 10.2	8.1 ± 8.5
Antipsychotic dose (CPZ equivalents in mg/day)	na	na	314.4 ± 188.6	373.4 ± 226.8
Psychotic disorder diagnosis (%)				
Psychotic disorder not otherwise specified	na	na	18.0	3.7
Paranoid schizophrenia	na	na	45.9	50.0
Residual schizophrenia	na	na	28.4	24.1
Undifferentiated schizophrenia	na	na	6.2	20.4
Schizophreniform disorder	na	na	1.5	1.9
PANSS (score)				
Positive	na	na	23.1 ± 6.8	22.3 ± 7.3
Negative	na	na	17.3 ± 6.7	17.6 ± 7.2
General	na	na	38.7 ± 7.5	38.4 ± 7.3
TMT-A direct scores (mean ± SD)	na	na	56.0 ± 29.5	56.8 ± 37.5

TMT: Trail Making Test, Direct scores expressed as time (sec).

2. Materials and methods

2.1. Subjects

2.1.1. Study 1. case-control sample

The cases involved in this study (N = 1193) included patients diagnosed with SZ according to DSM-IV criteria recruited from different hospitals across several regions in Spain. Healthy controls (N = 1839) were recruited from the same regions as the patients (Julià et al., 2014). For further details see Table 1 and Supplementary Material and Methods.

2.1.2. Study 2. neurocognition sample

We recruited 194 unrelated participants who were diagnosed as having SZ spectrum disorders according to the DSM-IV criteria. The Trail Making Test part A (TMT-A), administered as previously described (Martorell et al., 2007), was used as a measure of processing speed (Nuechterlein et al., 2004; Varjacic et al., 2018). The TMT-A scores (in seconds) are shown throughout the article, and higher values indicate lower PS. Further information on inclusion and exclusion criteria is provided in Supplementary Material and Methods.

2.1.3. Study 3. neuroimaging sample

Based on rs1264323 genotype, we selected 54 patients with a diagnosis of SZ from the Study 2 sample distributed as follows: 23 subjects with the rs1264323 GG allele, and 21 with the GA and 10 with the AA genotypes. The group with the rare homozygous AA genotype was limited to the 10 patients available. All patients were enrolled in a quantitative neuroimaging study based on DTI to assess whether the relationship between microscopic variations in WM could underlie the relationship between *DDR1* genotype and neurocognition. Further information can be found in Supplementary Material and Methods.

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2008. The study protocol and informed consent document were approved by the Hospital Universitari de Sant Joan (Reus, Spain) ethics committee. Informed consent of all the participants was obtained after the nature of the procedures had been fully explained.

2.2. Genotyping

DNA isolated from peripheral blood was used for SNP genotyping with TaqMan technology (genotyping details are available in Supplementary Material and Methods). SNPs rs1264323 and rs2267641, which influence *DDR1* isoform expression in the brain (Barbara Roig et al., 2012) and are associated with SZ (Roig et al., 2007), were genotyped. Moreover, rs3135388 (a proxy of HLA-DRB*1501 that has consistently been associated with multiple sclerosis (Cox et al., 2012)) and rs9268895 (near HLA-DRB9 and has been associated with SZ (Ripke et al., 2013)) were genotyped to exclude false locus associations.

2.3. Neuroimaging

Each subject in Study 3 underwent an MRI scanning session using a 1.5-T GE Signa scanner (General Electric Medical Systems). DTI data collection and fractional anisotropy (FA) image analysis protocols are described in Supplementary Material and Methods. To assess whether there was a link among *DDR1* genotype, PS and WM microscopic variation, we first localized those WM regions where FA correlated with PS, after which we checked whether FA in these regions showed differences between groups with different *DDR1* rs1264323 genotypes.

2.4. Statistical analysis

2.4.1. Study 1. case-control

Genotype frequencies in patients and controls were compared using Pearson's chi-square test. P-values adjusted using Bonferroni correction (2 SNPs analyzed simultaneously) were also calculated. Allele estimates, genotype association, and analysis of epistasis between SNPs were conducted using the software PLINK v1.07. We also evaluated the association between the SNP rs1264323 genotype and SZ using logistic regression, stratifying the sample by rs2267641C allele presence. The degree of association was represented as the odds ratio (OR) with the corresponding 95% confidence interval (CI). These analyses were conducted using SPSS Statistics Package, v22.0 (IBM Corp., New York, NY, USA).

2.4.2. Study 2. neurocognition

Categorical variables were reported as frequencies and percentages. Continuous variables were presented as the mean ± SD. We explored the normality of the distribution of continuous variables using the Kolmogorov-Smirnov test. TMT-A scores are shown in Figures and Tables, however, the normalized log-transformed variable was used in all statistical analyses. Parametric correlation coefficients were calculated to assess the associations between PS, symptoms (positive and negative scale scores and the general PANSS score) and other clinical variables (sex, age, years of education, duration of illness and antipsychotic dose). Student's *t*-tests were used to compare continuous variables stratified by sex. To compare PS between *DDR1* genotype groups, we conducted analysis of covariance (ANCOVA). *DDR1* genotypes were grouped following the dominant, recessive and codominant models and the groupings with the most statistically significant results are shown for clarity. We included as covariates the variables that correlated with cognitive function in the univariate and bivariate analyses (Supplementary Table 1). In addition, a bootstrap method (Dwivedi et al., 2017) was used because of the small size of the group homozygous for the minor allele. To assess whether *DDR1* genotype was associated with PS changes over time (the period between assessment for Study 2 and reassessment for Study 3), we conducted an ANOVA with repeated measures and appropriate covariables. These analyses were conducted using SPSS.

2.4.3. Study 3. neuroimaging

Whole-brain voxel-based statistical analyses were carried out using a general linear model by means of the Statistical Parametric Mapping (SPM12) software package (Wellcome Trust Centre for Neuroimaging, London, UK). The statistical model and contrasts of interest were designed to find regions where the FA values were positively or negatively correlated with PS based on TMT-A scores, the cognitive variable that was significantly associated with *DDR1* genotypes. Covariates were included to adjust for age and sex. Before the statistical analysis, normalized images were spatially filtered with a Gaussian kernel of FWHM = 2.5 mm. The statistical analysis was restricted to all voxels in WM (threshold: FA > 0.2). Regions were reported as significant at $p < 0.05$, fully corrected for multiple comparisons at the cluster level via the topological familywise error (FWE) approach implemented in SPM12 (based on random field theory) using a cluster-forming height threshold of $p < 0.001$ and a spatial extent threshold of $k > 40$ voxels. The anatomical locations of significant regions were determined with reference to the structural atlases integrated into MRIcron software, including the Automated Anatomical Labeling (AAL) structural atlas, the Johns Hopkins University (JHU) DTI-based white-matter atlas and the NatBrainLab tractography atlas. Finally, the average value of FA for all voxels in each significant cluster was extracted and further analyzed to check whether there were differences in FA between distinct genetic groups, as well as to ensure that the correlation between FA and PS was not due to potential confounding factors (age, sex, years of education, disease duration, PANSS score, or medication).

3. Results

3.1. Study 1. case-control replication study

A description of the study participants is shown in Table 1. Genotype frequencies, shown in Table 2, differed between cases and controls for rs1264323 (adjusted P = 0.015). Interestingly, a significant interaction between the SNPs rs1264323 and rs2267641 was observed (OR = 1.58, P = 0.00152). That is, carriers of one or two rs2267641C alleles who have an rs1264323 GA genotype are protected against the development of SZ (OR = 0.56; 95% CI = 0.40–0.77, P < 0.001) compared to rs1264323AA homozygous subjects. Therefore, an elevated risk of SZ is associated with rs1264323AA and one or two C alleles at rs2267641. In the present study, 8.3% of patients had the *DDR1* risk genotypes, compared to 5.2% of controls (Table 2). Together, these results demonstrate that the genetic association between *DDR1* and SZ is mediated by an interaction between rs1264323 and rs2267641.

One of the most replicated chromosomal regions associated with SZ is 6p21.3, near the MHC, which includes the human leukocyte antigen (HLA) genes (Corvin and Morris, 2014). To assess whether the observed associations between *DDR1* SNPs and SZ were due to or influenced by HLA genes, we assessed LD between *DDR1* SNPs (rs1264323 and rs2267641) and HLA-DRB*1501 (rs313538 associated with multiple sclerosis) and HLA-DRB9 (rs9268895, which has been associated with SZ). All LDs were low (r^2 < 0.04) (data not shown). Therefore, we assumed that the association between *DDR1* and SZ was independent of HLA genes.

3.2. Study 2. DDR1 and rs2267641 and TMT-A scores

Participants' general characteristics are summarized in Table 1. TMT-A scores, according to the model showing the most statistically significant differences, are shown in Table 3. In Model 1, subjects homozygous for the rs2267641C allele had elevated TMT-A scores (P = 0.001). Similarly, in Model 2, only subjects from AA-CC genotype group had significantly increased TMT-A scores (P = 0.009). Thus, patients with schizophrenia with the rs2267641CC genotype have elevated TMT-A scores that can be read as a sign of decreased PS and suggested a recessive effect of the C allele.

3.3. Study 3. DDR1 rs1264323, WM FA, and PS

Patient features, that were similar to those of Study 2, are summarized in Table 1. At a corrected p-value < 0.05, no significant regions of positive correlation between FA and TMT-A were found in the whole-brain analysis. By contrast, the analysis showed two clusters where FA was negatively correlated with TMT-A scores. One of these areas (cluster 1: corrected p-value = 0.006, cluster-size = 66 voxels, peak MNI coordinate (9,4,30), T-score = 4.59) was located in the body of the corpus callosum, reaching the margin of the right cingulum bundle. The second significant area (cluster 2: corrected p-value = 0.009, cluster-size = 61 voxels, peak MNI coordinate (32,-68,33), T-score = 4.96) was centered in a WM region in the right hemisphere close to the middle occipital gyrus, reaching the posterior segment of the arcuate fasciculus. For more details about the anatomical locations, see Fig. 1.

After the average FA value was computed for all voxels in both clusters, the ROI-based analysis revealed that the relationship between FA and PS remained significant (p = 0.007 and p < 0.001 for clusters 1 and 2) for a linear regression of PS by FA with the covariates of age, PANSS score and years of education, thus showing that the correlation between FA and PS was not due to any of the potential confounding factors that we investigated. Note that we had previously shown that these covariates (and not others) were independently associated with PS and that, although PS was not normally distributed (Shapiro-Wilk test p < 0.001), the residuals of the regression were normally distributed (Shapiro-Wilk test p = 0.581 and p = 0.964 for clusters 1 and 2).

Interestingly, we found that individuals with the genotype rs1264323AA showed lower FA in these clusters than individuals carrying the G allele (t-tests: p = 0.015 and p = 0.009 for clusters 1 and 2, respectively) (Fig. 1, panel D). FA in the second cluster showed a relationship with medication (p = 0.027), but medication was not found to be a confounding factor in a regression of FA by polymorphism covarying by medication (p = 0.015 and p = 0.007 for clusters 1 and 2). Thus, in these WM regions, individuals with the genotype rs1264323AA showed decreased FA; and decreased FA was associated with increased TMT-A scores (decreased PS). Moreover, we explored the involvement of the rs1264323 genotype in the differences in TMT-A scores between the first and second assessments, which on average were 6 years apart. The interaction between time and the rs1264323A allele was significantly associated (P = 0.029) with worsening of PS over time (Fig. 2, panels A and B). Together, these results showed that rs1264323 was associated with changes in FA in brain regions involved in PS in patients with SZ.

4. Discussion

4.1. Study 1

Here, we further demonstrated the association between *DDR1* and SZ in a case-control design using a Spanish sample. Moreover, we showed an interaction between rs1264323 and rs2267641 for the first time, producing a complex association with SZ. The data suggested that SZ was associated with the rs2267641C allele only in rs1264323A

Table 2
Genotype distribution (%) and multinomial logistic regression to assess the association between *DDR1* rs1264323 and rs2267641 and schizophrenia in patients and controls from Study 1 sample.

	Controls N = 1839	Patients N = 1193	Adjusted P[c]	
SNP				
rs1264323				
GG	47.2	49.3	0.015	
GA	44.2	39.7		
AA	8.7	11.0		
rs2267641				
AA	74.1	73.3	ns	
AC	24.4	24.9		
CC	1.5	1.9		
Combined genotype[a]			**Effect**	
GG-AA	47.2	49.3	Neutral	
GA-AA	23.4	21.3	Neutral	
AA-AA	3.4	2.8	Neutral	
GG-AC	0	0	NA	
GA-AC	**20.7**	**18.3**	**Protective**	
AA-AC	**3.7**	**6.4**	**Risk**	
GG-CC	0	0	NA	
GA-CC	0	0	NA	
AA-CC	**1.5**	**1.9**	**Risk**	
MLRA			**OR (95%CI)**	**P**
GG-AA/GA-AA[b]	95.4	96.2	1.2 (0.79–1.89)	**ns**
AA-AA	4.6	3.8		
GA-AC[b]	79.9	68.9	0.56 (0.40–0.77)	4×10^{-4}
AA-AC/AA-CC	20.1	31.1		

[a] rs1264323-rs2267641 combined genotype: rs1264323 GG, GA, AA; rs2267641 AA, AC, CC.
[b] Reference group in the multinomial logistic regression analysis (MLRA).
[c] Bonferroni correction.

Table 3
Analysis of covariance to compare mean TMT-A scores between carriers and non-carriers of the rs2267641 C allele in Study 2 sample.

Model 1[a]	Genotype rs2267641				P value	P value[c]
	AA + AC N = 190		CC N = 4			
TMT-A, mean ± SD	49.4 ± 1.5		66.7 ± 1.2		0.086	0.001
Model 2[b]	**Genotype rs1264323-rs2267641**					
	GG-AA **GA-AA** **AA-AA** N = 145	**GA-AC** N = 34	**AA-AC** N = 11	**AA-CC** N = 4	**P value**	**P value[c]**
TMT-A, mean ± SD	494 ± 1.5	49.4 ± 1.6	36.6 ± 1.3	66.7 ± .21	0.061[d]	0.009[d]

[a] The covariates included in the analysis (based on the bivariate analysis shown in Supplementary Table 1) were SNP rs1264323 (GG + GA vs AA), duration of illness, years of education, age at testing, gender, antipsychotic dose and PANSS Negative score.
[b] The covariates included in the analysis (based on the bivariate analysis shown in Supplementary Table 1) were duration of illness, years of education, age at testing, gender, antipsychotic dose and PANSS Negative score.
[c] ANCOVA using bootstrapping.
[d] Comparison AA-AC vs AA-CC.

homozygotes. We previously (Roig et al., 2007) identified the SNP rs1049623, which is in high LD with rs1264323 (examined in the present article), as being associated with SZ (OR = 1.44, 95% CI = 1.15–1.79, adjusted P = 0.0016). It is important to note that rs2267641 has not been included in most GWAS panels; therefore, genotype data on this SNP are scarce. Interestingly, rs2267641 is a functional SNP that has been implicated in the alternative splicing of *DDR1*b and *DDR1*c isoforms, and subjects with the rs2267641CC genotype had lower levels of *DDR1*b mRNA and higher levels of *DDR1*c mRNA in their brain tissue than subjects who were homozygous for the major allele (Barbara Roig et al., 2012b). Further, the levels of the *DDR1*c isoform were increased in patients with SZ compared with controls (Bàrbara Roig et al., 2012a). The epistatic interaction between rs1264323 and rs2267641 regarding the association with SZ, as observed in the present study, could involve differential isoform expression. Neither SNP causes an amino acid change, but both are involved in gene expression: rs2267641 because it alters the binding affinity of the A2RE mRNA sequence for the protein hnRNP A2 (Barbara Roig et al., 2012b), and rs1264323 that is included in the eQTL database (GTEx, http://www.gtexportal.org) for its differential expression in human tibial nerve ($P = 6.9 \times 10^{-5}$, n = 369) and other tissues, probably because of its position in the putative promoter region. Although we assumed that the association between *DDR1* and SZ was independent of HLA genes, HLA is a complex chromosomal region, and we cannot rule out the possibility that other variants linked to *DDR1* might influence the association that we have found. We must take into

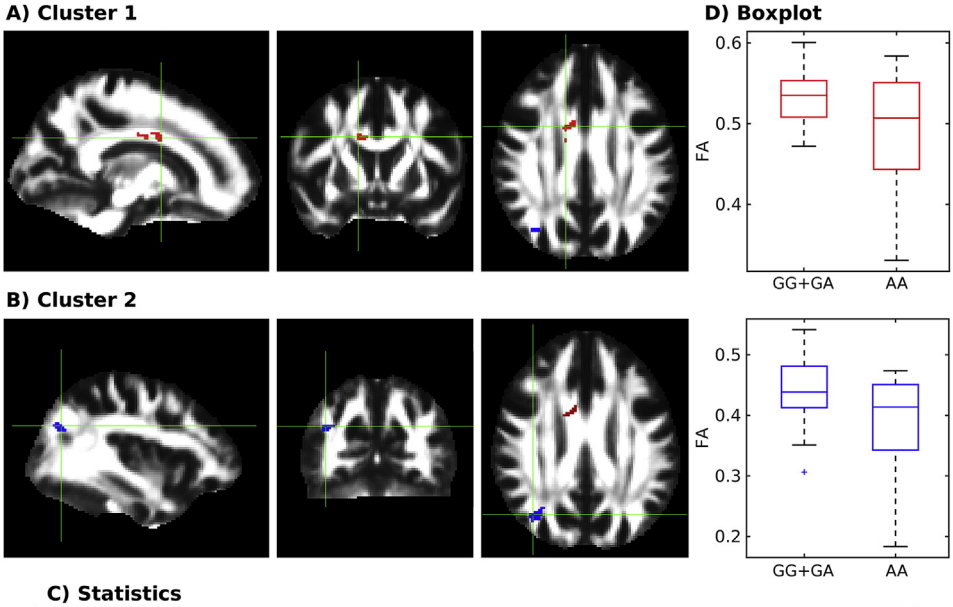
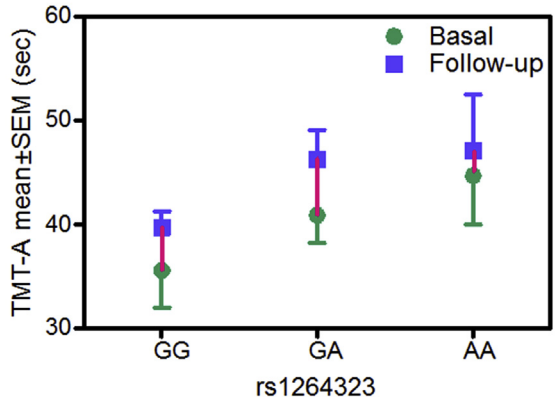


Fig. 1. Brain regions showing a significant correlation between processing speed (PS, TMT-A scores) and fractional anisotropy (FA) in patients with schizophrenia from Study 3. Panels A), B), and C) depict the anatomical locations and statistical results of the correlation analyses. Panel D) shows the intergroup comparisons between patients who were categorized by the presence of the rs1264323G allele.

A



B **Analysis of covariance with repeated measures to compare TMT-A direct scores between baseline and follow-up[a] according to rs1264232 genotype in Study 3 sample**

	Variables	P value
Between subjects effects[b]	rs1264323	0.884
Within subjects effects[b]	Time	0.054
	Time x rs1264323	0.029

[a]Mean time (years): 6.27±1.3.
[b]Covariates used: age, years of education, duration of illness, medication and negative symptoms.

Fig. 2. The time and rs1264323 effect on processing speed (PS, TMT-A scores) comparing baseline and follow-up measures in patients from Study 3. Panel A) shows a graph representing mean TMT-A scores (time, in seconds) according to rs1264323 genotype group at baseline and follow-up time points. Panel B) depicts the results from the analysis of covariance with repeated measures that compares TMT-A scores between baseline and follow-up according to rs1264323 genotype.

account that although the highest association with SZ ever found for a SNP is for rs9268895 near HLA DRB9 (Ripke et al., 2013), a significant risk was also observed for other genes not related to the immune system but located nearby (Corvin and Morris, 2014). Moreover, Bergen et al. (2012), using a Swedish sample, found a significant association between SZ and both SNPs at *LINCO00243*, which codes for a long mRNA and is located 50 kb upstream of *DDR1*.

4.2. Study 2

Through this study, we demonstrated a significant relationship between homozygosity for the rare rs2267641C allele and decreased PS in patients with SZ. There are no published studies on the relationship between *DDR1* and cognitive function. We know that the rs2267641C allele is associated with decreased abundance of the *DDR1*b isoform and increased abundance of the *DDR1*c isoform in whole brain tissue showing a genotype dose-dependent relationship (Supplementary Fig. 1, panel D) (Barbara Roig et al., 2012b), but further investigation is needed to elucidate the exact role of *DDR1* isoforms in brain physiology. However, these results are consistent with several published studies reporting that patients with abnormalities in oligodendrocyte genes show an increased severity of cognitive dysfunction. One example is a paper that reported the effects of genetic variants in oligodendrocyte genes (*CNP*, *MAG,* and *OLIG2*) on cognitive function and the involvement of myelin tract integrity (Voineskos et al., 2013).

4.3. Study 3

We found two clusters where FA was significantly correlated with PS. Notably, in these clusters patients with the genotype rs1264323AA showed lower FA than patients carrying the G allele. This result suggested that the G allele at rs1264323 may be protective, as it is associated with higher FA and thus with less damaged WM. This result is in line with the results of Study 1, in which we found that the G allele at rs1264323 is protective against SZ in subjects carrying the rs2267641C allele. *DDR1* is present in myelin (Bàrbara Roig et al., 2010); however, no detailed data exist about differential expression of *DDR1* across brain regions. A number of previous studies have found reduced FA in SZ (Kelly et al., 2018; Pomarol-Clotet et al., 2010), as well as correlations with symptomatology, sensory function, and cognition (Hoptman, 2010). Genetic susceptibility to reduced FA in healthy subjects has been found. For instance, four independent studies have reported that genetic variation in the *NRG1-ERBB4* complex, involved in axon guidance and myelination, is associated with reduced FA in WM, mainly affecting tracts from the frontal and temporal lobes (Konrad et al., 2009; McIntosh et al., 2008; Nickl-Jockschat et al., 2014; Winterer et al., 2008). Additionally, the rs1018381T allele of the *DTNBP1* gene was associated with differential FA compared to the A allele (Nickl-Jockschat et al., 2012). Different SNPs in *NTRK3*, related to oligodendrocyte and myelin development, were correlated with FA in several regions including the corpus callosum and the inferior longitudinal fasciculus (Braskie et al., 2013).

In SZ patients, an association appeared to exist between rs2710126, located inside *CNTNAP*, a protein involved in neuronal synchronization and brain connectivity, and FA in the uncinate fasciculus (Clemm von Hohenberg et al., 2013). A SNP of the *GRM3* gene was found to be correlated with FA in tracts from the cortico-cerebellar-thalamic-cortical circuit of patients with SZ (Mounce et al., 2014). Finally, a recent report showed that the *COMT* Val^{158}Met polymorphism moderates the association between WM microstructure and cognitive performance (Poletti et al., 2016).

The underlying neural mechanisms for the interindividual variability in PS remain unknown. It has been proposed that this variability may be due to differences in the physiological properties of the white matter in association fibers and tracts supporting interhemispheric transmission (Kochunov et al., 2017; Penke et al., 2010), such as the differences found in our study. For example, a mediation analysis carried out (Kochunov et al., 2017) using DTI data from 166 patients with schizophrenia found a significant association pathway from FA to PS to working memory. The strongest association was observed for the body of the corpus callosum, which contains interhemispheric motor and sensory fibers. Strong correlations were also observed for a number of association fibers including the cingulum bundle and the superior longitudinal fasciculus that contains the arcuate fasciculus. In two previous studies, the integrity of these tracts, as measured by DTI, was significantly associated with PS in healthy older people (Kerchner et al., 2012; Penke et al., 2010). PS and FA associations in the body of the corpus callosum have been found in other studies examining sickle cell anemia (Stotesbury et al., 2018), multiple sclerosis (Genova et al., 2013), and normal aging (Salami et al., 2012). Similar associations in the cingulum bundle have been reported in early-course schizophrenia (Seitz et al., 2016), normal aging (Salami et al., 2012) and adults with coronary artery disease (Santiago et al., 2015), the latter which also found a significant association in the inferior fronto-occipital fasciculus.

Data are scarce regarding the impact of genes on WM microstructure and PS. On the one hand, a number of neuroimaging studies in patients with SZ found that FA is strongly associated with PS (Karbasforoushan et al., 2015; Roalf et al., 2015; Zeng et al., 2016). On the other hand, a recent exploratory analysis provided preliminary data suggesting that *KCNQ1* may contribute to the correlated risks of diminished PS, diminished FA and SZ (Bruce et al., 2017).

All these previous studies highlighted the point that SZ is a very complex disorder involving multiple genes. The disruption of these genes is associated with local WM changes, which in turn, are related to different symptoms, as well as to sensorial and cognitive malfunction. In this context, our Study 3 provided new information about the involvement of *DDR1* in SZ and its relation to WM microstructure and PS.

Although we observed that DDR1 is present in myelin (Franco-Pons et al., 2009, 2006; B Roig et al., 2010 and speculated that it can modulate WM microstructure, DDR1 is present in activated leukocytes (Hachehouche et al., 2010; Kamohara et al., 2001) and therefore an involvement through brain tissue inflammation cannot be ruled out.

4.4. Strengths and limitations

One of the strengths of the present study is that we showed the association between *DDR1* and SZ through 3 different study designs: first, a case-control association analysis; second, a neuropsychological assessment in a cohort of SZ patients; and finally, a DTI neuroimaging study in a sample of SZ patients grouped according to *DDR1* genotype. Another strong point is the capacity to control for many confounding variables, such as the presence of psychotic symptoms, drug abuse, pharmacotherapy, and education. However, there is an important limitation regarding the sample size of the homozygous rare allele groups for both SNPs in Study 3. Future studies with larger sample size to allow detection the relationship between DDR1 variants and PS are required. Also new studies involving more SNPs in white matter genes and even polygenic risk scores to explore their influence in processing speed are worth conducting. FA, sensitive to changes in various microstructure parameters including axon diameter, degree of myelination, membrane permeability, fiber density, and orientation heterogeneity, is the most widely used metric to study WM in vivo. However, a potential limitation of this metric, apart from that we used a 1.5T platform to collect DTI scans, is that it is not specific to any of these parameters. Therefore, it is not possible to identify the particular aspect of the microstructure that is responsible for the FA changes (Beaulieu, 2002). For this reason, future studies should be conducted to explore more advanced neuroimaging techniques based on multiple MRI features (Canales-Rodríguez et al., 2014), allowing the individual characterization of these microstructural parameters (Daducci et al., 2015) by using MRI scanners with higher magnetic fields and stronger diffusion gradients (Jones et al., 2018).

5. Conclusions

First, we replicated the association of *DDR1* with SZ in an independent Spanish sample and demonstrated that a SNP-SNP interaction within *DDR1* played a role in the association with the disease. Second, we observed that SZ subjects with the rs2267641CC genotype had decreased PS scores. Third, SZ subjects with the rs1264323AA genotype showed decreased FA in WM regions in association with decreased PS. We conclude that *DDR1* variants may confer a risk of SZ through WM microstructural alterations leading to cognitive dysfunction.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2018.12.021.

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