


# Additive sex-specific influence of common non-synonymous *DISC1* variants on amygdala, basal ganglia, and white cortical surface area in healthy young adults

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**Abstract** The disrupted-in-schizophrenia-1 (*DISC1*) gene is known for its role in the development of mental disorders. It is also involved in neurodevelopment, cognition, and memory. To investigate the association between *DISC1* variants and brain morphology, we analyzed the influence of the three common non-synonymous polymorphisms in *DISC1* on specific brain structures in healthy young adults. The volumes of brain regions were determined in 145 subjects by magnetic resonance imaging and automated analysis using FreeSurfer. Genotyping was performed by high resolution melting of amplified products. In an additive genetic model, rs6675281 (Leu607Phe), rs3738401 (Arg264Gln), and rs821616 (Ser704Cys) significantly explained the volume variance of the amygdala ( $p = 0.007$ ) and the pallidum ( $p = 0.004$ ). A higher cumulative portion of minor alleles was associated with larger volumes of the amygdala ( $p = 0.005$ ), the pallidum ( $p = 0.001$ ), the caudate ( $p = 0.024$ ), and the putamen ( $p = 0.007$ ). Sex-

stratified analysis revealed a strong genetic effect of rs6675281 on putamen and pallidum in females but not in males and an opposite influence of rs3738401 on the white cortical surface in females compared to males. The strongest single association was found for rs821616 and the amygdala volume in male subjects ( $p < 0.001$ ). No effect was detected for the nucleus accumbens. We report—to our knowledge—for the first time a significant and sex-specific influence of common *DISC1* variants on volumes of the basal ganglia, the amygdala and on the cortical surface area. Our results demonstrate that the additive model of all three polymorphisms outperforms their single analysis.

**Keywords** Amygdala · Brain structures · Basal ganglia · *DISC1* · Genetic association studies · White cortical surface area

## Abbreviations

<i>DISC1</i>	Disrupted-in-schizophrenia 1
HRM	High resolution melting
MAF	Minor allele frequency
MRI	Magnetic resonance imaging
SNP	Single nucleotide polymorphism

## Introduction

Disrupted-in-schizophrenia-1 (*DISC1*) was first identified as a candidate gene for schizophrenia and other mental disorders by the detection of a chromosomal translocation in a large Scottish family (Blackwood et al. 2001). Several independent genetic linkage and association studies in diverse populations support these original linkage findings (Cannon et al. 2005; Szeszko et al. 2008; Nakata et al.

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2009) although the latest data of the Psychiatric Genomics Consortium dampen the expectations towards the role of *DISC1* compared to other identified candidate regions (Ripke and Consortium 2014). Genetic evidence now implicates the *DISC1* locus in susceptibility to schizophrenia, schizoaffective, bipolar and addictive disorders, major depression as well as various cognitive traits. A recent translational functional genomics study identified *DISC1* as a strong candidate gene for schizophrenia (Ayalew et al. 2012), which supports human brain imaging studies that suggest an effect of common *DISC1* variants on neurodevelopment, brain structure, and neurochemical function. However, it is not one of the common variants that appear to be risk markers for schizophrenia as indicated by a meta-analysis (Mathieson et al. 2012); rather, rare *DISC1* variants have been found to be associated with schizophrenia (Moens et al. 2011), bipolar spectrum disorders (Song et al. 2010), recurrent major depressive disorder (Thomson et al. 2014), opioid dependence (Xie et al. 2013) and autism (Crepel et al. 2010), which highlights the importance of studying subgroups of patients and identifying endophenotypes.

The moderately conserved *DISC1* gene encodes for a 94 kDa multifunctional scaffold protein of 854 amino acids and exhibits no significant sequence homology to other known proteins (Soares et al. 2011). *DISC1* appears to be involved in various processes during and after brain development including cell migration, neurite organization, cytoskeletal modulation, mitochondrial function, and signal transduction (Chubb et al. 2008; Brandon and Sawa 2011). This multitude of functions is accomplished via various binding partners of *DISC1*, such as NDEL, NDE1, PCM1, KIF5A, Kendrin, TNIK, ATF4, and PDE4B, which regulate fundamental cellular processes (Kamiya et al. 2012; Bradshaw and Porteous 2012). Consequently, *DISC1* interactors have also been defined as independent genetic susceptibility factors for psychiatric illness, such as *PDE4B* and *NDE1* for schizophrenia (Chubb et al. 2008).

In humans, the *DISC1* gene is located on chromosome 1q42 and spans approximately 415 kb (UCSC genome browser). The full-length transcript is supposed to consist of 13 alternatively spliced exons with a total size of 7.5 kb (Millar et al. 2000). The expression of *DISC1* is highly heritable and strongly regulated by *cis*- and *trans*-effects (Carless et al. 2011). Homologues have been identified in all major vertebrate families. Interestingly, the *DISC1* gene contains an antisense partner, *DISC2*, that is a putative noncoding RNA gene (Millar et al. 2000) with currently unknown function (Chubb et al. 2008). The presence and complexity of the many *DISC1* isoforms—over 40 differentially spliced transcripts have been identified in human brain tissues (Nakata et al. 2009)—is one of the reasons

that, so far, no traditional knockout mouse exists among the eight established distinct animal models for *DISC1* (Brandon and Kelly 2011).

In mouse models, altered expression of *DISC1* was associated with reduced brain cortical thickness, enlarged ventricles, and changes in dendritic arborisation (Johnstone et al. 2011) as well as the hippocampus (Kellendonk et al. 2009). Evidence from genetic and brain imaging studies in humans show a relationship between *DISC1* variants (single nucleotide polymorphisms, SNPs) and brain function in healthy subjects such as declarative memory (Callicott et al. 2005; Di Giorgio et al. 2008), verbal fluency (Prata et al. 2008), and cognitive aging (Thomson et al. 2005). Several volumetric studies have revealed effects of *DISC1* polymorphisms on brain structures including reduced hippocampal gray matter volume in rs821616 A (Ser) carriers (Callicott et al. 2005) and reduced volumes of the anterior cingulate cortical gray matter and the cingulate gyrus in rs821616 T (Cys) carriers (Hashimoto et al. 2006). Significantly less gray matter in the superior frontal gyrus and anterior cingulate gyrus was found in patients and healthy subjects carrying the rs6675281 T (Phe) allele compared to CC (Leu/Leu) homozygotes (Szeszko et al. 2008). An additive effect of the two most studied SNPs, rs821618 and rs6675281, on gray matter volumes has been suggested (Trost et al. 2013). Also, an independent and combined effect of rs821616 and rs6675281 was noted on cortical thinning in a longitudinal imaging study in healthy children and adolescents (Raznahan et al. 2011). Furthermore, the rs6675281 T carrier status seems to be associated with a trend-level increased surface in specific cortical areas (Chakravarty et al. 2012).

A number of further studies that predominantly focused on rs821616 and rs6675281 have found a genetic influence on various frontal, temporal, and parietal regions (summarized in Duff et al. 2013), albeit with sometimes inconsistent observations, results that yet lack replication, or results that are not robust to multiple-testing correction partially due to low numbers of subjects (Johnstone et al. 2011; Duff et al. 2013). Moreover, only Brauns et al. (2011) have detected a significant effect of the third non-conservative SNP within *DISC1*, rs3738401, namely on cortical thickness; they did not analyze the cortical surface area that is suggested to be under distinct genetic influence (Panizzon et al. 2009) and was found to be reduced in schizophrenic patients (Colibazzi et al. 2013). Concerning subcortical structures, bilateral alterations in striatal volume depending on the rs6675281 genotype among 54 healthy individuals of mixed sex have only recently been reported (Chakravarty et al. 2012). However, none of the studies analyzed the basal ganglia in more detail, although the interest in basal ganglia quantitative and qualitative morphology and function has recently increased due to

their apparent involvement in cognitive performance under healthy (Sandman et al. 2014; Burgaleta et al. 2014; Rhein et al. 2014a) and pathophysiological conditions (Mittal et al. 2010). Altered volumes or deformed basal ganglia structures have been found, for example, in autism (Estes et al. 2011; Wolff et al. 2013), obsessive–compulsive disorder (Choi et al. 2007), or schizophrenia (Hirjak et al. 2014). In addition, while there is evidence for a functional effect of *DISC1* on the nucleus accumbens from mutant mouse models particularly with respect to neurotransmitters and receptors (Lipina et al. 2013; Nakai et al. 2014; Kim et al. 2015), indications of an association of common *DISC1* variants with regional brain volumes is lacking in both animals and humans. Furthermore, despite a vast literature on amygdala volume abnormalities in schizophrenic patients (reviewed in Ganzola et al. 2014), the possible influence of *DISC1* variants on the amygdala has not yet been examined in detail.

In this study, we have, therefore, strived to analyze the genetic influence of *DISC1* on the volumes of the basal ganglia nuclei, the nucleus accumbens and the amygdala, as well as on the cortical surface area as determined by magnetic resonance imaging (MRI) in healthy young individuals. Among the high number of polymorphisms inside or in the proximity to *DISC1*, which are mostly intronic or synonymous polymorphisms, we have focused on the additive effect of the three common non-synonymous polymorphisms in *DISC1* because of their potential functional impact in vivo based on known independent in vitro functional consequences (Burdick et al. 2008; Narayanan et al. 2011; Eastwood et al. 2010; Malavasi et al. 2012; Singh et al. 2011): the two well-studied rs821616 (Ser704Cys) and rs6675281 (Leu607Phe) and also the less investigated rs3738401 (Arg264Gln). Special attention was given to possible sex-specific effects of the *DISC1* variants on brain structures.

## Materials and methods

### Study participants

Healthy volunteers ( $n = 156$ ) were recruited as part of the GENES study at the Friedrich-Alexander University Erlangen-Nürnberg. The study was approved by the local ethics committee (no. 3510) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave informed written consent after thorough explanation of the study prior to their inclusion, and they were financially compensated for their time. Subjects were between 18 and 35 years of age with similar academic backgrounds. They were of Caucasian-white ethnicity and

were eligible according to the following exclusion criteria screened using a self-report questionnaire: current or past medical history related to potentially affecting brain function such as head injury with loss of consciousness; neurological or psychiatric history of the individual or first degree relatives; alcohol or substance abuse (except for caffeine, nicotine and social alcohol consumption); birth complications; learning difficulties at primary school; history of heart or brain surgery; medication (except for hormonal contraceptives); current pregnancy or lactation; and any contraindications for MRI analysis.

The same sample has previously been analyzed for other parameters independent of *DISC1* (Sidiropoulos et al. 2011; Richter-Schmidinger et al. 2011; Alexopoulos et al. 2011; Rhein et al. 2014a, b; Reichel et al. 2014). The required sample size to detect differences in brain structures was calculated by power analysis from data available for *DISC1* polymorphisms and similar regions, i.e., the influence of rs6675281 on the left/right striatum, and the right occipital lobe surface area (Chakravarty et al. 2012) to be approximately between 68 and 72 individuals. In view of comparable studies on *DISC1* SNPs with sample sizes below 120 (Szeszko et al. 2008; Brauns et al. 2011; Trost et al. 2013) as well as our intention to additionally investigate sex-specific effects and a more favorable genotype ratio in our group, the GENES data set was judged suitable for the study aims.

Out of 156 participants, MRI scans were available and evaluated for 150 subjects. After exclusion of five further subjects for medical reasons identified only at the end of the examination, the remaining 145 (94 females and 51 males) were successfully genotyped for all three SNPs. Male volunteers (20–35 years) were only slightly, albeit significantly, older (18 months on average,  $p = 0.005$ ) than females (19–34 years; Online Resource 1). However, separate analysis of males and females subdivided into groups by genotype revealed no significant differences in age for either SNP. The majority of participants, 49 males (98 %) and 85 females (91 %), were right-handed—no data on handedness was available for two subjects.

### Genotyping

Genomic DNA was isolated from whole blood using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) according to the supplier's protocol. Genotyping of the *DISC1* polymorphism was performed using high resolution melting (HRM, Wittwer et al. 2003) by analyzing differences in the melting profile of small SNP-specific amplified fragments on a Roche LightCycler 480 (Roche Diagnostics, Mannheim, Germany). The following forward and reverse primers, annealing and melting curve temperatures were applied: AGGACCCGCGATGTCTCTCT and TCTG

CAGAGACCCGTGTAGC (58 bp; 60 °C; 74–90 °C) for rs3738401, CCCTTCTTCTCTCCACAACG and TCCA GCCCTTCTCTCTGATG (102 bp; 63 °C; 72–88 °C) for rs6675281, and TGGGAAGCTGACTTGGAAGC and CCTGGCTTCCTGGAGCTGTA (63 bp; 60 °C; 72–88 °C) for rs821616. For the HRM analysis, a polymerase chain reaction was set up containing 10 ng genomic DNA in 10 mM Tris/HCl pH 8.9, 50 mM KCl, 0.02 % Tween-20, 1.5 mM MgCl<sub>2</sub>, 200 μM dNTPs, 200 nM forward and reverse primers, and 0.1 unit Taq DNA polymerase (Rovalab, Teltow, Germany) in a total volume of 10 μl. Moreover, 0.5 μl EvaGreen (20× stock, Biotium, Hayward, USA) were added to the reaction to allow real-time quantification and subsequent detection of the melting curve by fluorescence analysis. After initial denaturation at 95 °C for 2 min, the template was amplified during 40 cycles of 12 s denaturation at 96 °C, 15 s annealing at the primer-specific temperature, and 15 s extension at 72 °C followed by a denaturation (2 min 95 °C) and re-annealing step (40 °C). PCR products were then slowly melted at 0.02 K/s under high resolution fluorescence recording (25 acquisitions/K). Quantitative evaluation and genotype analyses were performed with the gene scanning software (Roche Diagnostics, Mannheim, Germany). Data of samples not fulfilling a set of SNP-specific quality criteria with respect to Cq values or uniform fluorescence levels at the plateau phase were neglected, and the analysis was repeated. The correct assignment of melting curves to genotypes was confirmed for all three SNPs by sequencing the HRM product with the forward primer (rs6675281) or by sequencing a larger PCR product using the primers GCTGAGTCCCATTGCCAGAG (forward, rs3738401) or TCCAGCACAGTGCAGAGAGG (reverse, rs821616), respectively.

Differentiation of all three genotypes was achieved easily for rs6675281 (C/T), whereas the discrimination of both homozygous genotypes for rs3738401 (A/G) and rs821616 (A/T) required additional spiking reactions for homozygous samples with known homozygous control material. Again this resulted in a distinct heterozygous curve for samples that are homozygous for the other allele. The genotyping call rates of all three SNPs were 100 % (Table 1). The concordance for

more than 10 % duplicate samples was greater than 99 %. For the tests of the Hardy–Weinberg equilibrium (HWE), *p* values were all far above the conventional level of significance of 0.05 for the total group as well as for both sexes separately, indicating that our study population is close to genetic equilibrium and that systematic genotyping errors were unlikely (Table 1). Minor allele frequencies (MAF) were close to known frequencies for Utah residents with northern and western European ancestry from the CEPH collection population (CEU) from the HapMap Genome Browser (Table 1), who are most similar to our study group. In agreement with the low linkage disequilibrium ( $r^2 < 0.02$ , HapMap Genome Browser release #28 B36), the observed genotypes for the three SNPs were independent of each other.

### Magnetic resonance imaging

Brain MRI was successfully performed on 150 out of the 156 individuals. Axial FLAIR images with a slice thickness of 5 mm were first obtained to exclude any intracranial pathology as judged by an experienced neuroradiologist. Volumetric sagittal T1-weighted 3D sequence (magnetization-prepared rapid gradient echo, MPRAGE) images were acquired on a Sonata 1.5 T scanner (Siemens Healthcare, Erlangen, Germany) with a repetition time TR of 2030 ms, an echo time TE of 3.93 ms, a field of view = 290 × 290, a voxel size of 1 × 1 × 1 mm<sup>3</sup>, and a matrix size of 256 × 256 (144 slices). The T1-weighted images were next converted from DICOM to the NIfTI format. The FreeSurfer software (surfer.nmr.mgh.harvard.edu, version 5.1.0) was used as a free open source package of automated tools for the reconstruction of the brain's cortical surface and the creation of models of most macroscopically visible structures in the human brain from structural MRI data (Fischl 2012). These models subsequently served to determine volumes of brain regions using default values. To eliminate the inter-rater variability in manual edits, a fully automated approach with internal quality checks was applied when using the software. The steps included intensity and motion correction, transformation to the Talairach image space, intensity normalization, skull stripping, subcortical processing, and volumetric segmentation.

**Table 1** Genotype distribution for the three analyzed non-synonymous SNPs in 145 subjects

RefSNP	cDNA	Protein	Genotype frequencies (male/female)			<i>p</i> (Chi <sup>2</sup> test) for HWE			MAF	Ref MAF ( <i>n</i> )
			NN	Nn	nn	Male	Female	Total		
rs3738401	c.G791A	p.R264Q	19/37 (GG)	26/44 (AG)	6/13 (AA)	0.518	0.989	0.693	0.372	0.362 (224)
rs6675281	c.C1819T	p.L607F	35/74 (CC)	14/18 (CT)	2/2 (TT)	0.692	0.477	0.386	0.138	0.158 (222)
rs821616	c.A2110T	p.S704C	26/50 (AA)	23/37 (AT)	2/7 (TT)	0.258	0.966	0.529	0.269	0.331 (130)

The reference MAF is given for the CEU population from the HapMap Genome Browser release #28; the numbers of individuals are shown in brackets



FreeSurfer segmentation results from 32 randomly chosen subjects (20 %) were visually inspected by two independent researchers blinded with respect to the individuals' data. No errors were noted and thus no volume editing was performed. Duplicate analysis of three datasets with FreeSurfer starting from random seeds resulted in a high correlation of volume results with  $r = 0.999$ . Similarly, data obtained from duplicate independent scans of three individuals correlated with  $r > 0.995$ . The influence of individual differences in total brain size was eliminated by dividing all specific raw values by the intracranial volume (ICV) (O'Dwyer et al. 2012; Rhein et al. 2014a); thus, all these standardized volumes are without units.

Raw volume data for the basal ganglia regions caudate, putamen, and pallidum as well as for the nucleus accumbens, the amygdala, and also the cortical white surface area differed significantly between male and female subjects (Online Resource 1). The volumes in females were generally lower than in males. To account for sex differences, all evaluations with regard to genotypes were additionally performed separately by sex, even though volume disparities disappeared for some regions (except for volumes of the caudate nucleus and the hippocampus) after standardization to the ICV (Online Resource 1).

**Statistical analysis**

Statistical analyses were conducted using IBM SPSS Statistics 21 software (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism 5 (Graph Pad Software Inc., San Diego, CA, USA). Statistical tests were two-tailed with a significance level of  $p < 0.05$ . The Student's  $t$  test or the Wilcoxon–Mann–Whitney test were applied to calculate differences in age and brain volumes (Online Resource 1). Normal distribution and homoscedasticity were checked using the Kolmogorov–Smirnov test and Levene's test, respectively. Deviation of the obtained genotype frequencies from the Hardy–Weinberg equilibrium was calculated by the Chi-square test with one degree of freedom (Table 1). Since the three SNPs are not in linkage disequilibrium, they were regarded as independent variables.

For the analysis of the genetic influence of *DISC1* SNPs on brain structures (Tables 2, 3), hierarchical linear regression was performed with sex (coded by dummy variables) and age as the factors in the first step and with the three SNP genotypes (coded in order of increasing number of minor alleles because we assumed a gene-dosage effect: homozygous major allele = 1, heterozygous = 2, homozygous minor allele = 3) as additional factors in the second step to determine their additional contribution to the explanation of structural parameters by sex and age alone. The following indicators of the explanatory and predictive strength of these factors were

**Table 2** Analysis of polymorphisms' effects on standardized volumes of brain regions

Structure	Additive model			rs3738401 (p.R264Q)			rs6675281 (p.L607F)			rs821616 (p.S704C)			combined					
	$R^2$	$\Delta R^2$	$p(\Delta F)$	$B$	$p$	$p_B$	$p_{AB}$	$B$	$p$	$p_B$	$p_{AB}$	$B$	$p$	$p_B$	$p_{AB}$			
Caudate	0.157	0.041	0.083	0.041	0.598			0.132	0.095	(*)		<b>0.158</b>	<b>0.047</b>	*	(*)	0.178	<b>0.024</b>	*
Putamen	0.114	0.054	0.040	0.149	0.065	(*)	*	<b>0.164</b>	<b>0.044</b>	(*)	*	0.068	0.398			0.217	<b>0.007</b>	*
Pallidum	0.120	0.088	<b>0.004</b> *	<b>0.226</b>	<b>0.005</b>	**	**	<b>0.177</b>	<b>0.030</b>	(*)	*	0.053	0.514			0.266	<b>0.001</b>	**
Nucleus accumbens	0.048	0.003	0.921	0.050	0.605			-0.025	0.763			0.020	0.809			0.032	0.702	
Amygdala	0.086	0.083	<b>0.007</b> *	0.070	0.394			0.086	0.296			<b>0.274</b>	<b>0.001</b>	***	**	0.236	<b>0.005</b>	*
White cortical surface	0.039	0.022	0.370	0.059	0.479			0.009	0.916			0.139	0.100	(*)	(*)	0.118	0.157	

Results of linear regression analyses with sex and age in the first step and with the SNP genotypes (homozygous major allele = 1, heterozygous = 2, homozygous minor allele = 3) as additional factors in the second step of the additive genetic model to determine the  $R^2$ , the change in  $R^2$ , and the significance of the change in  $F$  (standardized coefficients beta ( $B$ ) and  $p$  values for  $p < 0.05$  in bold,  $s$  significant after correcting for multiple comparisons using Bonferroni post hoc tests for six primary hypotheses). To further support the results, levels for  $p_B$  values calculated from bootstrap analysis with 5000 resamples and for  $p_{AB}$  values from the analogous additive genetic allelic model (5000 resamples) are indicated as follows: (\*)  $p < 0.1$ , \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ . As an alternative to the three single SNPs, a combined genotype calculated as the cumulative score of individual genotypes was applied in the second step, and analogously the total number of minor alleles was used as a factor in the second step

**Table 3** Additive effect of *DISC1* polymorphisms in a sex-stratified analysis

Sex	Structure	Additive model			rs3738401 (p.R264Q)			rs6675281 (p.L607F)			rs821616 (p.S704C)			Combined			
		$R^2$	$\Delta R^2$	$p(\Delta F)$	$B$	$p$	$p_B$	$p_{aB}$	$B$	$p$	$p_B$	$p_{aB}$	$B$	$p$	$p_B$	$p_{aB}$	
Male	Caudate	0.102	0.078	0.276	-0.061	0.672		0.225	0.129	(*)	0.122	0.396	0.157	0.275			
	Putamen	0.061	0.026	0.737	0.135	0.366		0.054	0.720		0.082	0.578	0.155	0.280			
	Pallidum	0.114	0.094	0.196	0.259	0.077	(*)	0.141	0.337		0.129	0.365	<b>0.298</b>	<b>0.036</b>	(*)		*
	Nucleus accumbens	0.048	0.048	0.526	0.218	0.149		0.086	0.569		-0.013	0.931	0.156	0.283			
	Amygdala	0.246	0.245	<b>0.004</b>	-0.202	0.134		-0.049	0.715		<b>0.470</b>	<b>0.001</b>	**	0.167	0.251		(*)
Female	White cortical surface	0.135	0.077	0.264	-0.276	0.057	*	-0.027	0.853		-0.066	0.641	-0.209	0.137	*		(*)
	Caudate	0.129	0.048	0.191	0.119	0.242	(*)	0.081	0.431		0.176	0.084	(*)	<b>0.211</b>	<b>0.035</b>	*	*
	Putamen	0.159	0.089	<b>0.029</b>	0.136	0.173	*	<b>0.244</b>	<b>0.017</b>	*	0.083	0.403	<b>0.258</b>	<b>0.010</b>	*	*	*
	Pallidum	0.138	0.100	<b>0.020</b>	<b>0.200</b>	<b>0.049</b>	(*)	<b>0.214</b>	<b>0.038</b>	(*)	0.020	0.844	<b>0.257</b>	<b>0.011</b>	(*)	*	*
	Nucleus accumbens	0.075	0.002	0.982	-0.006	0.958		-0.033	0.752		0.020	0.849	-0.011	0.917			*
Amygdala	0.095	0.086	<b>0.044</b>	<b>0.206</b>	<b>0.048</b>	(*)	0.104	0.321		0.191	0.067	*	<b>0.292</b>	<b>0.005</b>	*	*	
White cortical surface	0.128	0.110	<b>0.014</b>	<b>0.234</b>	<b>0.023</b>	*	0.036	0.728		<b>0.251</b>	<b>0.015</b>	**	<b>0.308</b>	<b>0.003</b>	*	*	

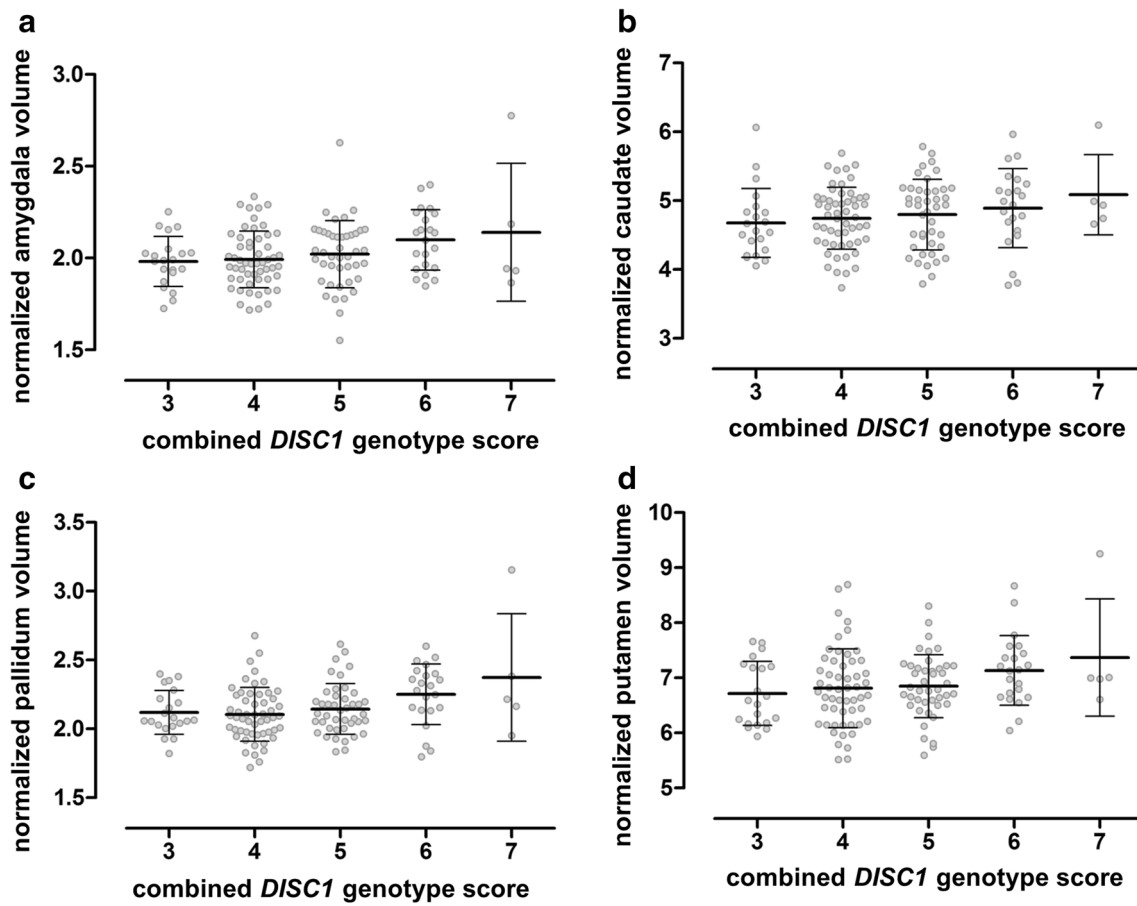
Results of linear regression analysis performed as in Table 2 separately for male and female subjects (see Table 2 for explanation of symbols)

calculated:  $R^2$  (with  $R$  as the correlation coefficient) to indicate what proportion of the total variation in the dependent variable can be explained by the independent variables, the incremental change in  $R^2$  from the first to the second step, the significance of the change in  $F$  (with  $F$  resulting from the  $F$  test of the significance of the regression equation),  $p(\Delta F)$ , standardized beta coefficients (beta weight,  $B$ ) as a unitless indication of the magnitude and direction of the contribution of a variable calculated as the regression coefficient after conversion of independent and dependent variables to standardized  $z$  scores, and  $p$  values. To test the primary hypothesis of an additive genetic effect on the brain volumes, the  $p$  values were corrected with respect to multiple testing performed by conservative Bonferroni post hoc tests for the six statistical models of the brain structures (Table 2). Afterwards, we explored further associations without statistical correction for multiple testing. Unless otherwise indicated, nominal  $p$  values are given in the text and tables. To substantiate the findings in the absence of an independent replication sample, we calculated  $p_B$  values using a bootstrap analysis (5000 resamples, bias corrected and accelerated method). Moreover, we have defined a cumulative genotype score as the total sum of individual genotype codes (homozygous major allele = 1, heterozygous = 2, homozygous minor allele = 3) to condense the information from the three SNPs, and we then applied this single parameter in the second step of the linear regression analysis. Furthermore, linear regression was repeated with alleles as factors (major allele = 0 vs. minor allele = 1). The analysis was additionally performed separately for male and female subjects to identify sex-specific effects. Statistical power analysis was conducted by applying the free G\*3Power analysis tool 3.1.9.2 (Faul et al. 2007) using the conventional values of  $\alpha = 0.05$  and  $1 - \beta = 0.80$ . Values in supplemental tables represent the mean  $\pm$  standard deviation.

## Results

### Additive effect of *DISC1* genotypes on the basal ganglia and the amygdala

According to our main hypothesis, we have used linear regression to analyze the combined genetic effect of rs6675281 (Leu607Phe), rs3738401 (Arg264Gln), and rs821616 (Ser704Cys) on the six specific brain structures. In the additive genetic models, the three polymorphisms contributed significantly to the volume variance of the amygdala [ $\Delta R^2 = 0.083$ ,  $p = 0.007$ , Bonferroni-adjusted  $p$  value for multiple testing of 0.043 (six primary hypotheses)] and the pallidum ( $\Delta R^2 = 0.088$ ,  $p = 0.004$ , adjusted 0.025) and with nominal significance to the



**Fig. 1** Association of the combined cumulative genotype score for the three analyzed *DISC1* SNPs (rs3738401, rs6675281, and rs821616) with normalized brain volumes of the amygdala (a), the caudate (b), the pallidum (c), and the putamen (d). The graphs show the median with the 25/75 percentiles and all individual ( $n = 145$ )

volume variance of the putamen ( $\Delta R^2 = 0.054$ ,  $p = 0.040$ ). We subsequently analyzed the influence of individual SNPs and revealed effects of multiple polymorphisms with the highest significance and standardized beta for rs821616 and the amygdala ( $B = 0.274$ ,  $p = 0.0011$ , Table 2) that would survive conservative correction for multiple testing if a total of 24 analyses [(3 SNPs + 1 additive model)  $\times$  6 brain regions] was taken into account.

Although studies on other brain structures have not shown common trends for the direction of the association of the minor or major allele with specific volumes or cortical thickness (Duff et al. 2013), all associations of the three SNPs on the caudate, putamen, pallidum, and amygdala in our study were unidirectional, i.e., the minor alleles were associated with larger structures as indicated by the positive standardized beta coefficients (Table 2). We have, therefore, constructed a cumulative genotype score as the total sum of individual genotype codes (homozygous major allele = 1, heterozygous = 2, homozygous minor

values. To avoid a false positive observation possibly caused by outliers, e.g. a female individual with the combined *DISC1* genotype score 7, we used ranked normalized brain volume data to recalculate the effects as suggested by Conover and Iman (1982). All  $p$  values remained below 0.05

allele = 3). In this combined model, a higher score representing a larger cumulative portion of minor alleles was associated with larger volumes of the amygdala, the pallidum, the caudate, and the putamen ( $p < 0.05$ , Table 2; Fig. 1). Additionally, linear regression analysis for the additive genetic effects of the three SNPs at the allelic level confirmed or even strengthened the reported observations for individual SNPs as well as for the combined score ( $p_{aB}$  in Table 2).

### Sex specific effects of *DISC1* variants on basal ganglia and amygdala volumes

The mean standardized brain volumes and surface data for the three SNP genotypes revealed a similar allele dosage trend in males and females for most but not all structures whenever genotype specific differences were apparent (Online Resource 2). Therefore, additional independent linear regression analysis was performed for male and female subjects with age as a known confounder. In

females, the three *DISC1* SNPs (genotype code) as independent variables in the second linear regression model significantly affected the volumes of the putamen, the pallidum, the amygdala, and the white cortical surface with contributions from different SNPs ( $p < 0.05$ , Table 3). Age proved to be a strong influencing parameter particularly for the caudate, putamen, and pallidum ( $p < 0.05$ ) in females. For males, the addition of SNPs improved the model only for the amygdala volume ( $p = 0.004$ ).

At the level of individual SNPs, sex-stratified analysis revealed a strong genetic effect (based on beta values) of rs6675281 on the putamen and pallidum in females but not in males. The strongest single correlation was found for the rs821616 minor allele with larger amygdala volumes in male subjects ( $B = 0.470$ ,  $p = 0.0008$ ). Here, the standardized volume of the amygdala was 20 % larger in TT homozygous ( $2.33 \pm 0.08$ ,  $n = 2$ ) compared to AA homozygous individuals ( $1.95 \pm 0.16$ ,  $n = 26$ ) with intermediate levels in AT heterozygotes ( $2.07 \pm 0.19$ ,  $n = 23$ ). The largest difference in females, 16 % of mean values between subjects homozygous for the major and minor allele, respectively, was observed for the rs6675281 and the putamen.

Application of the single combined genotype score resulted in nominally significant  $p$  values and a strong beta coefficient above 0.2 for the caudate, the putamen, the pallidum, the amygdala, and the white cortical surface in females and for the pallidum in males (Table 3). Additional linear regression with SNPs at the allelic level led to similar  $p$  values. To support the truly additive effect of the polymorphisms, linear regression was performed, and each SNP was added individually in the second step with age as a covariate. In all five models—amygdala for males and females as well as putamen, pallidum, and cortical white surface in females—the corrected  $R^2$  integrating all three SNPs exceeded that of each single polymorphism's influence.

Taken together, all three SNPs predicted to different extents brain structural size in male and female subjects with more brain regions affected in female individuals (Table 3). Moreover, size differences for the basal ganglia and amygdala volumes and white cortical surface area between individuals with the lowest and the highest cumulative genotype score were all above 10 % for females with an average of 15 % compared to 4 % average size difference in males (Online Resource 3).

### Sex-specific opposite effect of *DISC1* variants on the white cortical surface

The white cortical surface area was the only analyzed structure with an opposite directional influence of *DISC1*

SNPs in males and females. The minor alleles of all three polymorphisms—most notably rs3738401 ( $B = -0.276$ ,  $p = 0.057$ )—were associated with a smaller cortical white surface area in males whereas the same minor alleles were associated with a larger surface area in females ( $B = 0.234$ ,  $p = 0.023$  for rs3738401).

### No effect of *DISC1* variants on the volume of the nucleus accumbens

Analysis of the influence of the three *DISC1* variants on the volume of the nucleus accumbens did not reveal any significant or trend-like effect neither in the additive model nor at the level of individual SNPs (all  $p > 0.6$ , Table 2). Moreover, there were also no convincing sex-specific associations of genotypes with the volume when analyzing male and female subgroups separately (Table 3).

### Replication of *DISC1* variant effects on hippocampal volume and cortical thickness to validate the data set

We have used the previously reported influence of rs821616 on hippocampal volume (Callicott et al. 2005) and cortical thickness (Raznahan et al. 2011) to validate our volumetric data set. In agreement with the study by Callicott et al. on 158 healthy Caucasians with significantly reduced hippocampal gray matter in A (Ser) homozygotes compared to T (Cys) homozygotes, we observed the lowest standardized hippocampal volumes for AA (males  $5.37 \pm 0.44$ ,  $n = 26$ ; females  $5.65 \pm 0.46$ ,  $n = 50$ ), the intermediate volumes for AT (males  $5.43 \pm 0.47$ ,  $n = 23$ ; females  $5.71 \pm 0.46$ ,  $n = 37$ ), and the highest volumes for TT (males  $5.72 \pm 0.01$ ,  $n = 2$ ; females  $6.00 \pm 0.55$ ,  $n = 7$ ) for both sexes. These differences failed to reach significance in our analysis ( $p = 0.056$  for the whole group).

In a longitudinal imaging study of 255 typically developing individuals aged 9–22 years, the rate of cortical thinning varied with the *DISC1* genotype, and both rs6675281 and rs821616 SNPs influenced the cortical thickness mostly with a spatially specific effect (Raznahan et al. 2011). Although not significant, our data for both sexes separately and combined conform to the report of larger cortical thickness in the rs6675281/rs821616 CC/T-carrier group ( $2.60 \pm 0.09$  mm,  $n = 51$  for the whole set) versus smallest values in the C-carrier/AA haplotype group ( $2.58 \pm 0.10$  mm,  $n = 18$ ). Besides the weak influence of rs821616 on cortical thickness in our female subsample, we also observed a weak effect of rs3738401 exclusively in females ( $B = 0.188$ ,  $p = 0.072$ ) that was not noted in the mixed study group of Brauns et al. (2011).



## Discussion

In our study, we examined the additive and SNP- and sex-specific influences of all three non-synonymous *DISC1* polymorphisms on brain structures and have found previously not reported considerable combined effects on regions of the basal ganglia, the amygdala, and the white cortical surface. These results extend first observations of an additive effect of rs821616 (Ser704Cys) and rs6675281 (Leu607Phe) (Troost et al. 2013; Raznahan et al. 2011) to the third non-synonymous and the less studied SNP rs3738401 (Arg264Gln). We show that the additive model including all three SNPs outperforms single SNP analysis in explaining brain structural variance. An approach similar to our cumulative score as an indication of the number of minor alleles was recently successfully applied to predict case–control status by a cumulative risk profiling score extending to alleles from different genes that had shown modest associations with schizophrenia in a discovery genome-wide association study (Ripke and Consortium 2014).

In line with our primary hypotheses we have observed additive genetic effects for the putamen ( $\Delta R^2 = 0.054$ ), the pallidum ( $\Delta R^2 = 0.088$ ), and the amygdala ( $\Delta R^2 = 0.083$ , Table 2). The latter two remained significant even after conservative correction for multiple testing. To our knowledge, this is the first reported association of *DISC1* variants with the amygdala volume. One previous finding of a relationship between *DISC1* rs16854756 and the left pallidum volume (Carless et al. 2011) supports our result. We performed a literature search to detect genes relating to both *DISC1* and the amygdala or the pallidum volumes to substantiate this finding. Although there are indications for genetic liability effects for the pallidum (Yang et al. 2012), no specific genetic determinants have been detected so far. Previously identified genetic factors influencing the amygdala volume include allelic variations in the stathmin (*STMN1*) and serotonin transporter (*SLC6A4*) genes (Stjepanovic et al. 2013), the *OXTR* rs2254298 (Furman et al. 2011), variations of the MAO-A VNTR (Cerasa et al. 2011), the NMDAR NR2A subunit (*GRIN2A*) (Inoue et al. 2010), *BDNF* (Montag et al. 2009), and the 5-*HTTLPR* polymorphism (Scherk et al. 2009); however, none of the proteins encoded by these genes appear to be a direct interaction partner of *DISC1*, and they thus seem to affect the amygdala via other mechanisms.

We proceeded with SNP-specific subanalyses of the effects since there is evidence for independent functional consequences of the analyzed non-synonymous SNPs on their respective proteins: Ser704Cys (rs821616) alters the binding pattern to its competing interactors NDEL1 and NDE1 (Burdick et al. 2008) and exhibits higher-order self-

oligomerization (Narayanan et al. 2011). Variants Ser704Cys and Leu607Phe (rs6675281) modulate centrosomal localization of the binding partner PCM1 in glial cells (Eastwood et al. 2010). Moreover, the Leu607Phe variant located in a predicted conserved leucine zipper disrupts *DISC1* nuclear targeting, weakens its inhibitory effect on ATF4-dependent transcription, and ablates its modulatory effect on transcriptional responses to endoplasmic reticulum stress (Malavasi et al. 2012). *DISC1* variants Arg264Gln (rs3738401) and Leu607Phe both disrupt canonical Wnt/glycogen synthase kinase 3 beta signaling and neural progenitor cell proliferation while Ser704Cys inhibits neuronal migration (Singh et al. 2011). In concordance with these different cellular functions, the individual SNPs appear to exert specific effects on brain structures. For example, we have obtained evidence for an impact of rs6675281 on the volume of the putamen. This agrees with a previously reported association of this SNP with the striatal volume by Chakravarty et al. (2012). Despite its biological effects, the rs3738401 has so far attracted little attention in brain morphological studies. We have detected an impact of this variant on the volume of the pallidum and hence suggest to include this SNP in further investigations.

It is tempting to assume that the found brain volume differences are mediated by the amino acid substitutions of the *DISC1* variants. However, we are cautious since no full-length or even partial experimental 3D structures of *DISC1* are available; even biophysical characterization of the full-length protein is mostly still lacking (Chubb et al. 2008). Other effects such as on RNA stability or folding, accessibility to miRNA, or influence on alternative splicing as observed for rs821616 and rs6675281 (Nakata et al. 2009) could also play a role. While it is unlikely, that these non-synonymous SNPs influence *DISC1* gene expression levels, it would be worthwhile to investigate other genetic and epigenetic markers with an influence on *DISC1* gene regulation.

We attempted to minimize sex-specific effects by standardization of all volumes to ICV. Unexpectedly, some of the observed associations were still sex-dependent—they were either limited to one sex or they were even reversed for male and female subjects such as for the white cortical surface. An indication for a sex difference is also provided by the detection of a larger white matter surface area of the right hemisphere in males compared to females independent of disease status as schizophrenic or healthy (Colibazzi et al. 2013). Our data support the observation of a larger striatum for carriers of the rarer rs6675281 T allele that was reported for a mixed group of 54 volunteers (Chakravarty et al. 2012). However, we found the association of rs6675281 and volume of the putamen as part of

the striatum exclusively in the female subgroup. Moreover, we detected an influence of rs6675281 on the adjacent structure, the pallidum, in females that was weaker in males. In general, in our cohort the effect of the combined minor allele genotype score was particularly evident in females ( $B > 0.2$  for five structures in females vs.  $B > 0.2$  only for the pallidum in males, Table 3) which might suggest a stronger genetic determination of the analyzed brain structures in females by *DISC1*. This is supported by observations of a sex-dependent association of intelligence in childhood with volumes of the basal ganglia and striatum (MacDonald et al. 2014) and sexual dimorphisms of healthy adult human brain volumes such as the amygdala (Goldstein et al. 2001). We speculate that the investigated *DISC1* gene variant effects on brain structures are modulated by sex hormone-guided cerebral organization during early neurodevelopment. Undoubtedly, trajectories of maturational and aging effects vary considerably over different cortical structures (Sowell et al. 2003).

While our analysis profits from the homogeneity of the study groups concerning age and educational background—we have selected predominantly medical students aged 19–35—future studies should determine whether the observed effects hold true for a broader age spectrum as well as for individuals with diverse educational attainment. The difference in group size between males and females might have introduced some bias concerning the interpretation of sex-specific results. A further limitation of our study concerns the restricted resolution of the 1.5 T MRI scans utilized for analysis. Additionally, the method of volumetric measurement by the FreeSurfer software might have weakened effects. However, this automated parcellation method shows a high reliability for cortical and subcortical metrics (Liem et al. 2015) and has been cross-validated in healthy and diseased individuals (Desikan et al. 2006). Authors report generally a high correlation and similar atrophy patterns, albeit with some specific discrepancies between manual, semi-automated, and automated segmentation analyses (Lehmann et al. 2010; Oscar-Berman and Song 2011). Although the correction of raw volumes for the ICV itself and the applied algorithm are debatable (Sanfilipo et al. 2004) and connected to the risk of introducing noise and reducing power, this standardization has been chosen in this study as a widely accepted method in the literature for the analysis of subcortical structures (Bickart et al. 2011; Wolff et al. 2013; Hibar et al. 2015).

Although our sample size appeared appropriate based on power analysis and was comparable to similar studies, the relatively low number of 145 subjects limits the validity of our findings and ultimately requires replication in a larger sample also keeping in mind the need for precaution in drawing conclusions from a single genetic

association report as illustrated by reviews and meta-analyses (Hirschhorn et al. 2002; Ioannidis et al. 2001). Moreover, the logical consequence of our results is to investigate the influence of the *DISC1* variants on brain functions associated with these structures, i.e., to genotype individuals from behavioral or cognitive studies with respect to *DISC1* SNPs. Based on our data for the amygdala and subcortical nuclei of the basal ganglia system, we could expect to find effects on traits such as social interactions (Bickart et al. 2011), emotional learning, working memory, and memory consolidation (McIntyre et al. 2003). We have already observed an additive effect of three polymorphisms on several brain structures. Thus, the analysis of further polymorphisms inside or in proximity to *DISC1* that also include rare variants (Thomson et al. 2014) with possible independent contributions via the protein's various interaction partners could even strengthen the overall genetic effect of *DISC1*. Additional genotyping for common variants at further loci such as those recently found to influence subcortical brain structures including the amygdala, caudate, pallidum, and putamen (Hibar et al. 2015) is expected to further increase the observed combined genetic effect.

Taken together, we confirmed our primary hypothesis of an additive genetic effect of common *DISC1* variants on the volume of the amygdala, the putamen, and the pallidum in healthy young adults. Moreover, our results suggest SNP- and sex-specific effects on brain structures including the caudate and the white cortical surface area as well as the less investigated rs3738401. Finally, this study illustrates the advantage of the combined analysis of the three SNPs in an additive genetic model.

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#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** The study was approved by the local ethics committee (No. 3510) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave informed written consent prior to their inclusion in the study.

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