NeuroImage 57 (2011) 1591–1600

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

DISC1 is associated with cortical thickness and neural efficiency

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ARTICLE INFO

Article history:
Received 1 February 2011
Revised 19 April 2011
Accepted 19 May 2011
Available online 27 May 2011

Keywords:
Cortical thickness
Single nucleotide polymorphism
DISC1
Functional MRI
Working memory
Schizophrenia

ABSTRACT

Background: Disrupted in schizophrenia 1 (DISC1) is known to play a major role during brain development and is a candidate gene for schizophrenia. Cortical thickness is highly heritable and several MRI studies have shown widespread reductions of cortical thickness in patients with schizophrenia. Here, we investigated the effects of variation in DISC1 on cortical thickness. In a subsequent analysis we tested whether the identified DISC1 risk variant is also associated with neural activity during working memory functioning.
Methods: We acquired structural MRI (sMRI), functional MRI (fMRI) and genotype data from 96 healthy volunteers. Separate cortical statistical maps for five single nucleotide polymorphisms (SNP) of DISC1 were generated to detect differences of cortical thickness in genotype groups across the entire cortical surface. Working-memory related load-dependent activation was measured during the Sternberg Item Recognition Paradigm and analyzed using a region-of-interest approach.
Results: Phe allele carriers of the DISC1 SNP Leu607Phe had significantly reduced cortical thickness in the left supramarginal gyrus compared to Leu/Leu homozygotes. Neural activity in the left dorsolateral prefrontal cortex (DLPFC) during working memory task was increased in Phe allele carriers, whereas working memory performance did not differ between genotype groups.
Conclusions: This study provides convergent evidence for the effect of DISC1 risk variants on two independent brain-based intermediate phenotypes of schizophrenia. The same risk variant was associated with cortical thickness reductions and signs of neural inefficiency during a working memory task. Our findings provide further evidence for a neurodevelopmental model of schizophrenia.

Introduction

Schizophrenia is highly heritable and first-degree relatives of patients exhibit up to an 18 fold increased risk of also developing clinically meaningful schizophrenia symptoms (Tandon et al., 2008). Linkage and association studies suggest a variety of genetic risk variants associated with the disease (Straub and Weinberger, 2006) but Disrupted in Schizophrenia 1 (DISC1) is one of the most promising candidate genes (Chubb et al., 2008). Two nonsynonymous common single nucleotide polymorphisms (SNP) within the DISC1 gene have been well studied — Leu607Phe (rs6675281) and Ser704Cys (rs821616). The Phe allele of Leu607Phe has been associated with elevated risk for schizophrenia (Cannon et al., 2005; Hodgkinson et al., 2004), a greater severity of positive symptoms and volume reductions in the superiorfrontal and anterior cingulate gyrus (Szeszko et al., 2008). Similarly, variation within the DISC1 Ser704Cys SNP was associated with increased risk for the disease and also with hippocampal volume in healthy controls as well as gray matter volumes in other brain regions (Callicott et al., 2005; Szeszko et al., 2008; Takahashi et al., 2009).

DISC1 expression has been detected in human, primate and mouse brain tissue (Austin et al., 2004; Lipska et al., 2006). It has been observed in both, neurons but also in glial cells (Seshadri et al., 2010). In a mouse model, DISC1 protein expression has been demonstrated to be a dynamic process with two major peaks corresponding to the time periods of embryonic neurogenesis and puberty, which fits well with neurodevelopmental models of schizophrenia (Marenco and Weinberger, 2000; Schurov et al., 2004). Although many functional aspects of DISC1 remain to be investigated, various neurobiologically relevant DISC1–protein interactions have been found, which demonstrate DISC1's role in brain development processes (Brandon et al., 2009). For example, a recent study suggests that DISC1 mediates

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doi:10.1016/j.neuroimage.2011.05.058

neuronal progenitor cell proliferation by regulating GSK3β/β, a serine/threonine protein kinase (Mao et al., 2009). It is also known that DISC1 protein interaction with LIS1, NDEL1 and NDE1 impairs neuronal migration, neurite outgrowth and the development of the cerebral cortex (Brandon et al., 2009; Kamiya et al., 2005). In addition to its relevance during early neuronal development, DISC1 is important for synaptic functioning in late development and the adult brain (Hayashi-Takagi et al., 2010; Wang et al., 2010).

Despite the identification of DISC1 as an important risk factor for schizophrenia via linkage and association studies, attempts to replicate those associations have often failed (Chubb et al., 2008). One possible explanation is that top-level symptoms or psychiatric diagnoses are too distal from the underlying pathogenesis of the disorder to provide sufficient power to detect underlying genetic diatheses. Consequently, there is an ongoing search for objective brain-based measurable traits, or intermediate phenotypes, that decompose top-level phenotypes into meaningful markers more proximally related to genetic aspects of schizophrenia (Allen et al., 2009). Such markers should be present in unaffected first-degree relatives of patients, even in the absence of clinically meaningful symptoms (Gottesman and Gould, 2003).

We chose cortical thickness as our primary neuroimaging phenotype of interest because (i) patients with schizophrenia show widespread reductions in cortical thickness in frontal, temporal and parietal regions as measured by structural magnetic resonance imaging (sMRI) (Goldman et al., 2009; Schultz et al., 2010), and (ii) sibling and family sMRI studies provide evidence for the heritability of cortical thickness measures (Gogtay et al., 2007; Goldman et al., 2009; Winkler et al., 2010) suggesting that this aspect of cortical anatomy may represent a reliable intermediate phenotype for schizophrenia (Gottesman and Gould, 2003). Moreover, the aforementioned heritability studies indicate that cortical thickness and surface area should be considered separately and preferred over gray matter volume (which is a combination of thickness and surface parameters) in genetic imaging studies (Panizzon et al., 2009; Winkler et al., 2010).

Due to the recent development of novel techniques (http://surfer.nmr.mgh.harvard.edu) we were able to estimate cortical thickness at about 320.000 points (vertices) across both hemispheres instead of limiting our analyses to any a priori region of interest. This approach allows for spatially non-biased examination of our hypothesis.

Objective

Using MRI and genetic data from the Mind Clinical Imaging Consortium (MCIC) study, we aimed to test whether common variants of DISC1 are associated with regional cortical thickness which was modeled across the entire cortex. Given the prior results of a relationship between DISC1 and hippocampus volume we estimated genotype effects of DISC1 on hippocampus volume in an additional analysis. We found an association of Leu607Phe and cortical thickness in the left supramarginal gyrus which is part of the inferior parietal lobule. Because of the known role of the inferior parietal lobule in cognitive and executive functioning and the implication of the frontoparietal network in working memory performance (Buchsbaum et al., 2005; Champod and Petrides, 2010; Salgado-Pineda et al., 2003; Torrey, 2007) we also tested the effects of Leu607Phe on behavioral performance and neural activity during a working memory paradigm conducted during functional MRI (fMRI) scans.

Methods

Participants

The MCIC study of schizophrenia (Ehrlich et al., 2010; Roffman et al., 2008) obtained structural and functional MRI data on a total of 328 subjects (160 patients with schizophrenia and 168 healthy controls) from four participating sites: Universities of Iowa (UI), Minnesota (UMN), New Mexico (UNM) and Massachusetts General Hospital in Boston (MGH). In this study we included 97 healthy controls who had complete MRI and genotype data (Table 1). In order to characterize the effects of DISC1 variants on brain structure, we decided to include only healthy controls, because subtle genetic effects on cortical thickness may be masked by subsequent environmental insults to the brain (Hulshoff Pol and Kahn, 2008). In particular, antipsychotic medication has been shown to promote widespread changes in cortical thickness and subcortical volumes (Navari and Dazzan, 2009; Scherk and Falkai, 2006; Tomelleri et al., 2009). Participants were excluded if they had a history of neurological or psychiatric disease, history of a head injury, history of substance abuse or dependence within the past month, severe or disabling medical conditions, contraindication to MR scanning or IQ less than 70 (based on the reading subtest from the WRAT-IIIRT). All participants were further required to be at least 18 and no older than 60, and to be fluent in English. After complete description of the study to the participants, written informed consent was obtained. The human subjects research committees at each of the four sites approved the study protocol.

Table 1
Basic demographics are presented according to genotype. We included all subjects who had complete MRI and genotype data (n = 97 for rs1322784 and rs11122359, n = 96 for Leu607Phe , n = 93 for Ser704Cys and n = 89 for Arg264Gln). Abbreviations: #H, Number of minor allele homozygotes; WRAT, Wide Range Achievement Test; SES, socioeconomic status; handedness, Annett Handedness Scale; UI, University of Iowa; MGH, Massachusetts General Hospital; UMN, University of Minnesota; UNM, University of New Mexico. One way ANOVA did not show any significant main effects of genotype groups (minor allele carriers vs. major allele homozygotes) on age, WRAT Score, parental SES and handedness. Chi-square statistics did not reveal any relationships between genotype groups (minor allele carriers vs. major allele homozygotes) and gender. The Fisher exact test did not show any relationships between genotype groups (minor allele carriers vs. major allele homozygotes) and ethnicity. Chi-square statistics (Fisher exact test in cases of small sample sizes of minor allele carriers) did not reveal any relationships between genotype groups (minor allele carriers vs. major allele homozygotes) and acquisition site.

		N (#H)	Gender		Ethnicity		Age		WRAT score		Parental SES		Handedness	
			Female		White		Mean	SD	Mean	SD	Mean	SD	Mean	SD
SNP	Allele		N	%	N	%								
rs1322784	T/T	62	24	38.7	57	91.9	33.06	10.86	50.89	4.37	2.51	0.81	1.37	3.25
	C carriers	35 (4)	17	48.6	30	85.7	33.19	11.55	50.56	4.01	2.81	0.65	0.92	2.62
rs11122359	G/G	46	19	41.3	40	87	34.98	10.86	51.15	3.61	2.76	0.74	0.87	2.51
	A carriers	51 (9)	22	43.1	47	92.2	31.49	11.45	50.27	4.56	2.65	0.72	1.2	3.12
Leu607Phe	Leu/Leu	72	27	37.5	66	91.7	32.78	11.21	50.6	4.17	2.65	0.63	1.28	3.2
	Phe carriers	24 (3)	13	54.2	20	83.3	32.79	11.36	50.75	4.04	2.88	0.95	0.54	1.38
Ser704Cys	Ser/Ser	55	27	49.1	52	94.5	33.44	11.61	51.04	4.43	2.58	0.71	1.24	3.17
	Cys carriers	38 (7)	14	36.8	32	84.2	31	9.82	50.18	3.76	2.76	0.68	0.76	2.48
Arg264Gln	Arg/Arg	42	18	42.9	40	95.2	32.33	11.04	49.79	4.01	2.64	0.76	0.64	2.08
	Gln carriers	47 (9)	22	46.8	40	85.1	32.87	10.88	51.19	4.18	2.64	0.67	1.49	3.54

Clinical measures

Before starting the study, clinicians from all four sites participated in a two-day training session, during which cross-site inter-rater reliability for the primary diagnostic and symptom-rating scales was established (85% concordance with videotaped training materials). All study participants underwent an extensive clinical diagnostic assessment that included either the SCID-I/P or NP (First et al., 2002) or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Premorbid cognitive achievement was estimated by the Wide Range Achievement Test (WRAT-IIIRT (Wilkinson, 1993)); parental socioeconomic status (SES) was determined using the Hollingshead index (Hollingshead, 1965) and handedness was determined using the Annett Scale of Hand Preference (Annett, 1970).

Sternberg Item Recognition Paradigm

The Sternberg Item Recognition Paradigm (SIRP) permits the assessment of the maintenance and scanning components of working memory (Manoach et al., 1999). During SIRP performance, neural activation increases as a function of working memory load (Manoach et al., 2000). Participants practiced the paradigm before scanning until they understood the task well enough to perform at a greater-than-chance level of accuracy. Briefly, in each block a memory set, one (1t), three (3t), or five (5t) digits, were presented. This Encode phase was followed by a presentation of 14 digits, one at a time (the Probe phase) and participants responded to each probe to indicate whether or not the probe digit was in the memory set. For more details see SM 1.1.

Structural and functional image acquisition

Structural MRI data was acquired with either a 1.5T Siemens Sonata (UNM, MGH, UI) or a 3T Siemens Trio (UMN). Also, functional MRI data was acquired with either a 1.5T Siemens Sonata (UNM) or a 3T Siemens Trio (UI, MGH, UMN). The T1-weighted structural brain scans at each of the four sites were acquired with a coronal gradient echo sequence: TR = 2530 ms for 3T, TR = 12 ms for 1.5T; TE = 3.79 for 3T, TE = 4.76 ms for 1.5T; TI = 1100 for 3T; Bandwidth = 181 for 3T, Bandwidth = 110 for 1.5T; 0.625 × 0.625 voxel size; slice thickness 1.5 mm; FOV, 256 × 256 × 128 cm matrix; FOV = 16 cm; NEX = 1 for the 3T, NEX = 3 for the 1.5T.

For all sites, functional images were acquired by using single-shot echo-planar imaging with identical parameters [orientation: AC–PC line; number of slices = 27; slice thickness = 4 mm, 1-mm gap; TR = 2000 ms; TE = 30 ms (3T) or 40 ms (1.5T), FOV = 22 cm; matrix 64 × 64; flip angle = 90°; voxel dimensions = 3.44 × 3.44 × 4 mm]. Cross-site calibration and reliability was established prior to the study (Jovicich et al., 2006; Jovicich et al., 2009; Yendiki et al., 2010).

Structural and functional image data processing

Structural MRI data from three consecutive volumes were registered, motion corrected, averaged and analyzed in an automated manner with the atlas-based FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu, Version 4.0.1). This process included volumetric segmentation and cortical surface reconstruction. The cortical surface reconstruction was performed for each hemisphere and included tessellation of the gray matter/white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Fischl et al., 1999). Final surfaces were used to calculate cortical thickness at each vertex on the tessellated surface as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary (Fischl and Dale, 2000). Segmentation and surface reconstruction quality were assured by manual inspection of all raw MRI volumes, segmented volumes in three planes and pial as well as inflated volumes. Five participants' MRI data failed the aforementioned quality assurance. The data of these subjects were then recovered with minor manual intervention. All research staff involved in the processing of imaging data was blind to genotype.

We evaluated the quality of the fMRI data by manual inspection and using artifact detection tools (ART) (Whitfield-Gabrieli, 2009). Functional images were processed using the FBIRN Image Processing Stream (FIPS), a pipeline utilizing the FMRIB Software Library of FSL. A Functional Imaging Linear Model (FILM (Woolrich et al., 2001)) was fit to model the Probe phases of each subject's preprocessed functional time series. We used the following linear Contrasts of Parameter Estimates (COPEs): Probe-5t versus Probe-1t and any load (Probe-1t or Probe-3t or Probe-5t) versus fixation. Here we refer to responses to the Probe-5t versus Probe-1t condition as "load-dependent" activation.

We obtained indices of activation for the DLPFC and supramarginal gyrus ROIs using the COPEs obtained from the second-level fixed-effects analysis for each participant. We applied an additional functional mask, based on the COPE of any load (1t, 3t or 5t) versus fixation exceeding a threshold of Z = 2.3 and extracted the maximum percent signal change (Max%Δ), defined as the maximum COPE of Probe-5t versus Probe-1t. Additional details are included in SM 1.2.

Genotyping

We genotyped the following DISC1 SNPs: rs1322784, rs11122359, Arg264Gln (rs3738401), Ser704Cys (rs821616) and Leu607Phe (rs6675281). These SNPs represent an informative subset of a larger number of known DISC1 SNPs used in a prior genetic association and imaging genetics studies (Cannon et al., 2005; Chubb et al., 2008; Hennah et al., 2003; Hennah et al., 2005; Hodgkinson et al., 2004; Rastogi et al., 2009; Thomson et al., 2005). Please refer to SM 1.3 for specific assay IDs.

Statistical analyses

Each SNP or haplotype was tested in a separate statistical model. Following the approach taken in previous studies (Callicott et al., 2005; Di Giorgio et al., 2008; Hashimoto et al., 2006; Szeszko et al., 2008) we decided to consider homo- and heterozygous carriers of the minor allele as one group.

Entire cortex vertex wise analyses of cortical thickness were performed with FreeSurfer contrasting carriers of the minor allele vs. homozygotes of the major allele. Briefly, spherical cortical thickness data from all subjects were mapped to an average subject (http://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage). Cortical thickness maps were smoothed using a Gaussian kernel with a full-width-at-half-maximum of 10 mm. Finally, general linear models (GLM) were run for each SNP at all vertices (n = 163,842) per hemisphere. In line with similar studies, we included age, gender and acquisition site into the models as control variables (Goldman et al., 2009; Kuperberg et al., 2003; Narr et al., 2005; Salat et al., 2004; Schultz et al., 2010). All cortical thickness results were corrected for multiple comparisons using a Monte-Carlo simulation. This procedure includes the following steps: (1) an initial vertex-wise threshold (VWT) was set to p = 0.001 to form spatially contiguous areas of association (referred to as "cluster"). (2) The likelihood that a finding (cluster) of this size and magnitude (difference in thickness as specified by the VWT) would appear by chance, i.e. when using repeated random sampling, was tested using Monte-Carlo simulation with 10,000 repeats. This results in a cluster-wise probability (CWP), which is reported using p-values

throughout the results section. Uncorrected results are not reported. In order to control for false positive results due to population stratification or due to brain asymmetry caused by handedness we reran all models on a sample limited to the majority ethnicity (white participants n = 84) and right-handed participants (n = 84).

In addition, we performed three exploratory analyses. First, all Monte Carlo simulations were repeated using a more liberal initial VWT of p = 0.05. Second, a haplotype analysis, based on haplotype block estimation with Haploview in the white subgroup using a variant of the four gamete rule was carried out (Barrett et al., 2005; Wang et al., 2002). We found one haplotype block, which included the DISC1 SNPs Leu607Phe and rs11122359. For this haplotype block we found three haplotypes with a frequency >10%: CA, CG and TG (the haplotype TA was only found in 0.009% of all participants). These haplotypes were used as regressors in additional general linear models predicting cortical thickness. Third, we tested whether any of the 5 SNPs would account for a significant portion of variance in hippocampus volumes. A series of independent regression analyses included the 5 aforementioned DISC1 SNPs (carriers of the minor allele vs. homozygotes of the major allele), and also controlled for age, intracranial volume, gender and acquisition site.

In subsequent analyses we tested the functional significance of our main finding from the cortical thickness analysis. Therefore we measured the effects of the Leu607Phe SNP on average SIRP accuracy as well as neural response to increasing working memory difficulty using linear regression analyses and covarying for age, gender and acquisition site. Neural response was modeled for right and left DLPFC as well as the left supramarginal gyrus. Further information is included in SM 1.4.

Results

Sample characteristics

The observed genotype frequencies of the five DISC1 SNPs did not deviate from HWE (p>0.05). Demographic variables did not differ by any of the five DISC1 genotype groups (Table 1) and Chi-square statistics did not reveal any relationships between genotype groups and acquisition site (all p values>0.05).There were significant differences in age and parental SES between the four acquisition sites ($F = 2.942$, $df = 95$ $p = 0.037$ and $F = 8.573$, $df = 95$ $p < 0.001$). As shown in Table 2 participants from MGH were on average older than those from UI. Participants from UNM showed a lower parental SES than those from MGH and UI. Otherwise, participants did not differ in gender, ethnicity, age, WRAT Score, parental SES and handedness across sites.

Cortical thickness — main analyses

Overall, 607Phe carriers showed reduced cortical gray matter thickness in an area corresponding to the left supramarginal gyrus compared to Leu homozygotes (Fig. 1, CWP = 0.0008). The average thickness in this cluster region was 2.62 mm for Leu homozygotes and 2.38 mm for Phe carriers (a reduction of 9.23%). Please refer to SM 1.3 for details about the calculation of these average thickness measures. Our result could be confirmed in subanalyses restricted to dextral and white participants (CWP = 0.0004 and CWP = 0.0044). None of the other DISC1 SNPs showed significant associations with cortical thickness at a conservative VWT of 0.001 in our sample. Our main finding – the association of the Leu607Phe polymorphism with cortical thickness – is still significant after applying an additional conservative Bonferroni correction for the number of individually tested SNPs (n = 5, adjusted CWP = 0.05/5 = 0.01).

Cortical thickness — exploratory analyses

Monte Carlo simulation with a more liberal initial VWT of 0.05 revealed further findings (see Fig. 2). C allele carriers of rs1322784 showed a reduced cortical thickness compared to T homozygotes in the superior temporal (CWP = 0.0194) and the lingual (CWP = 0.0265) gyrus. G homozygotes of rs11122359 showed a reduced cortical thickness compared to carriers of the A allele in the pericalcarine and cuneus region (CWP = 0.0001). Ser homozygotes of Ser704Cys showed a reduced thickness in the left superiorfrontal gyrus (CWP = 0.04225), whereas the Cys allele was associated with reduced cortical thickness in the right lateral occipital gyrus (CWP = 0.0237). Gln carriers of the Arg264Gln polymorphism showed a reduced cortical thickness compared to Arg homozygotes in the lateral occipital gyrus (CWP = 0.0186).

A haplotype (Leu607Phe, rs11122359: TG) that included the Phe allele of Leu607Phe was also associated with reduced cortical gray matter thickness in the left supramarginal gyrus (Figure SM 1) while no DISC1 genotype effects on hippocampal volumes were observed (Table 3).

Working memory performance and neural activity — effects of Leu607Phe

At the behavioral level (% accuracy during working memory task performance) there was no difference between Phe allele carriers and Leu homozygotes (Load1 − T = −0.9, df = 93, p = 0.377; Load3 − T = −1.4, df = 93, p = 0.158; Load5 − T = −0.407, df = 93, p = 0.685 Fig. 3A). However, Phe allele carriers showed a significantly higher neural activity with increasing memory load in the left DLPFC during the same working memory paradigm (beta = −0.295, df = 88, p = 0.005; Fig. 3B). Neural

Table 2
Basic demographics are presented for 96 healthy volunteers that had complete MRI and Leu607Phe genotype data according to acquisition site. Abbreviations: WRAT, Wide Range Achievement Test; SES, socioeconomic status; handedness, Annett Handedness Scale; UI, University of Iowa; MGH, Massachusetts General Hospital; UMN, University of Minnesota; UNM, University of New Mexico. One way ANOVA and when appropriate Tamhane post hoc tests were performed to detect significant differences of age, WRAT Score, parental SES and handedness between acquisition sites. Chi-square statistics (Fisher exact test in cases of small sample sizes) were performed to detect significant relationships between acquisition site and gender as well as between acquisition site and ethnicity; *,p<0.05; a — participants from MGH had a significantly higher age than those from UI (p = 0.012); b — participants from MGH had significantly higher parental SES than those from UNM (p = 0.001); c — participants from UI had significantly higher parental SES than those from UNM (p = 0.011).

Site	N	N	Gender		Ethnicity		Age		WRAT score		Parental SES		Handedness	
			Female		White		Mean	SD	Mean	SD	Mean	SD	Mean	SD
			N	%	N	%								
UI		53	23	43.4	50	94.3	30.66[a]	10.4	50.32	4.21	2.85[b]	0.41	0.96	3.01
MGH		17	9	52.9	11	64.7*	39.65[a]	9.27	51.47	4.32	3[c]	1.06	1.41	3.36
UMN		13	5	38.5	13	100	32.54	11.85	50.08	4.21	2.54	0.78	0.54	0.88
UNM		13	3	23.1	12	92.3	32.69	13.44	51.38	3.5	1.92[b,c]	0.64	1.77	2.98
Total		96	40	41.7	86	89.6	32.78	11.19	50.64	4.12	2.71	0.72	1.09	2.87

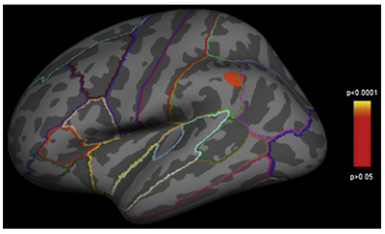

Fig. 1. Cortical statistical map illustrating the region of reduced cortical thickness in Phe carriers of the SNP Leu607Phe compared to Leu homozygotes. This map is shown on the inflated surface of the standard average subject, allowing visualization of data across the entire cortical surface without interference from cortical folding. The CWP-value (CWP = 0.0008 corrected for multiple comparisons) is represented according to the color code.

activity in the left supramarginal gyrus or the right DLPFC did not differ by Leu607Phe status ($\beta = 0.133$, $df = 88$, $p = 0.198$ and $\beta = -0.149$, $df = 88$, $p = 0.154$). There was no association between working memory performance and neural activity in any of these regions (Table SM 1).

Discussion

Using a surface-based analysis to examine the relationship between genotype effects of DISC1 variants and cortical thickness, we demonstrate a robust association of cortical gray matter thickness reductions in the left supramarginal gyrus and a known schizophrenia risk variant of DISC1 (the Phe allele of the Leu607Phe polymorphism). The supramarginal gyrus, the rostral region of the inferior parietal lobule, is part of the heteromodal association areas which also include the DLPFC, Broca's area and the superior temporal gyrus (Pearlson et al., 1996). These cortical areas form higher-order networks of neural circuits, mediating multimodal sensory processes and executive functioning and are implicated in core symptoms of schizophrenia, such as working memory dysfunction and positive symptoms (Broome et al., 2009; Maruff et al., 2005; Wible et al., 2009). Schizophrenia patients have been reported to show reduced cortical thickness and abnormal neural activity in these brain regions (Narr et al., 2005; Schultz et al., 2010). Interestingly, carriers of the risk variant (Phe) also recruited more neural resources within the left DLPFC during a working memory task although performance was similar across groups.

Our exploratory analysis at a more liberal threshold revealed further associations between DISC1 and cortical thickness with smaller effect sizes. These additional results underscore the complexity of DISC1 gene expression on the regional organization of cortical thickness. Our results suggest that some associations may represent localized genotypic effects where one variant and the associated protein interactions influence different brain areas in distinctive ways.

During embryonic development neuronal progenitor cells migrating from the marginal zone of the telencephalic vesicle cause the cortex to thicken (Narr et al., 2005). Cortical thickness is assumed to reflect the arrangement and density of neuronal and glial cells as well as passing axons (Parent and Carpenter, 1995). Postmortem studies in patients with schizophrenia showed reduced neuronal size and a decrease in interneuronal neuropil, dendritic trees and cortical afferents (Harrison, 1999; Selemon and Goldman-Rakic, 1999) while no reduction in the number of neurons or signs of gliosis could be demonstrated (Selemon and Goldman-Rakic, 1999; Thune et al., 2001). Therefore it can be hypothesized, that neurodevelopmental processes such as neurogenesis, neurite outgrowth, neuronal migration, differentiation and synaptogenesis as well as the genes which control these processes (such as DISC1) are major determinants of cortical thickness which might modulate the risk for schizophrenia in young adulthood (Akbarian et al., 1993; Arnold, 1999; Jakob and Beckmann, 1986). The Leu607Phe polymorphism is one of the few coding variants to be associated with schizophrenia-related phenotypes and our study further supports this view, though direct evidence on how this SNP alters DISC1 molecular behavior and how this could affect neurodevelopmental processes is still lacking. Recent reports however suggest that the interaction between DISC1 and pericentriolar material 1 (PCM), which plays an important role in the microtubule organization, is affected by the Leu607Phe polymorphism. DISC1-PCM co-localization and neurotransmitter release are reduced in Phe607 cells compared to Leu607 cells (Eastwood et al., 2009). In mouse models, the disruption of DISC1-PCM co-localization causes delayed migration of neurons into the developing cortex (Kamiya et al., 2008). Another study found an association between the Phe allele and different short splice mRNA variants of DISC1 in brain and lymphocyte cells. Of note, schizophrenia patients were shown to have an elevated cerebral expression of these mRNA variants which may interrupt important DISC1–protein interactions (Nakata et al., 2009).

Interestingly, DISC1 has been previously associated with the volume of the supramarginal gyrus in schizophrenia patients (Takahashi et al., 2009). However, Takahashi et al found a relationship with the Ser704Cys polymorphism and a direct comparison of their results to ours is limited by the different methodological approaches and genetic background of the two samples. The Ser704Cys polymorphism has also been linked to hippocampal volume. In the first study Ser homozygotes showed decreased hippocampal volumes (Callicott et al., 2005). In another investigation the Cys carriers showed a trend towards reduced hippocampal volumes (Di Giorgio et al., 2008) whereas three subsequent studies (including our own) could not find significant relationships between this polymorphism and hippocampal volume (Hashimoto et al., 2006; Takahashi et al., 2009). These inconsistent results are difficult to reconcile and might arise from possible genetic and allelic heterogeneity within different populations. The Ser704Cys polymorphism may not be the SNP which is causally related to changes in hippocampus volume but rather tag various haplotypes with diverse effects on hippocampal cortical architecture (Callicott et al., 2005). Furthermore, exon 11 of DISC1 that includes Ser704Cys undergoes alternative splicing and encodes for a region of the protein that interacts with several other proteins (Chubb et al., 2008; Di Giorgio et al., 2008).This may result in various cellular and neurodevelopmental effects of the DISC1 Ser704Cys polymorphism.

Regional reduction of cortical thickness in the parietal lobe may also be related to dysfunctional neuronal networks subserving working memory. Working memory, which is impaired in schizophrenia, is best described as the ability to hold information in an active state for a short period of time (Goldman-Rakic, 1994; Green et al., 2000; Manoach, 2003). Many of the prominent cognitive and behavioral deficits of schizophrenia can be conceptualized as a consequence of disrupted working memory. For example, disorganized speech and thought processes could be a manifestation of the inability to maintain a linguistic schema in mind. According to a large number of animal and human studies, working memory depends on the integrated function of a neurocognitive network comprising spatially distributed regions in the bilateral prefrontal and parietal cortices (Chafee and Goldman-Rakic, 2000; Constantinidis and Procyk, 2004; Owen et al., 2005; Quintana et al., 2003; Wager and Smith, 2003; Woodward et al., 2006). Neuroimaging studies on working memory disruption in schizophrenia and their unaffected relatives have pointed to abnormal brain activation patterns that comprise hypo- or hyperactivation of prefrontal and parietal brain regions, depending on the paradigm and the level of performance (Glahn et al., 2005; Kim et al., 2009b; MacDonald et al., 2009; Manoach, 2003; Tan et al., 2007; Thermenos et al., 2005). Furthermore, there is growing evidence that structural and functional connections between the frontal and parietal cortices are important for working memory performance and that these connections might be disturbed in schizophrenia (Honey et al., 2002; Karlsgodt et al., 2008;

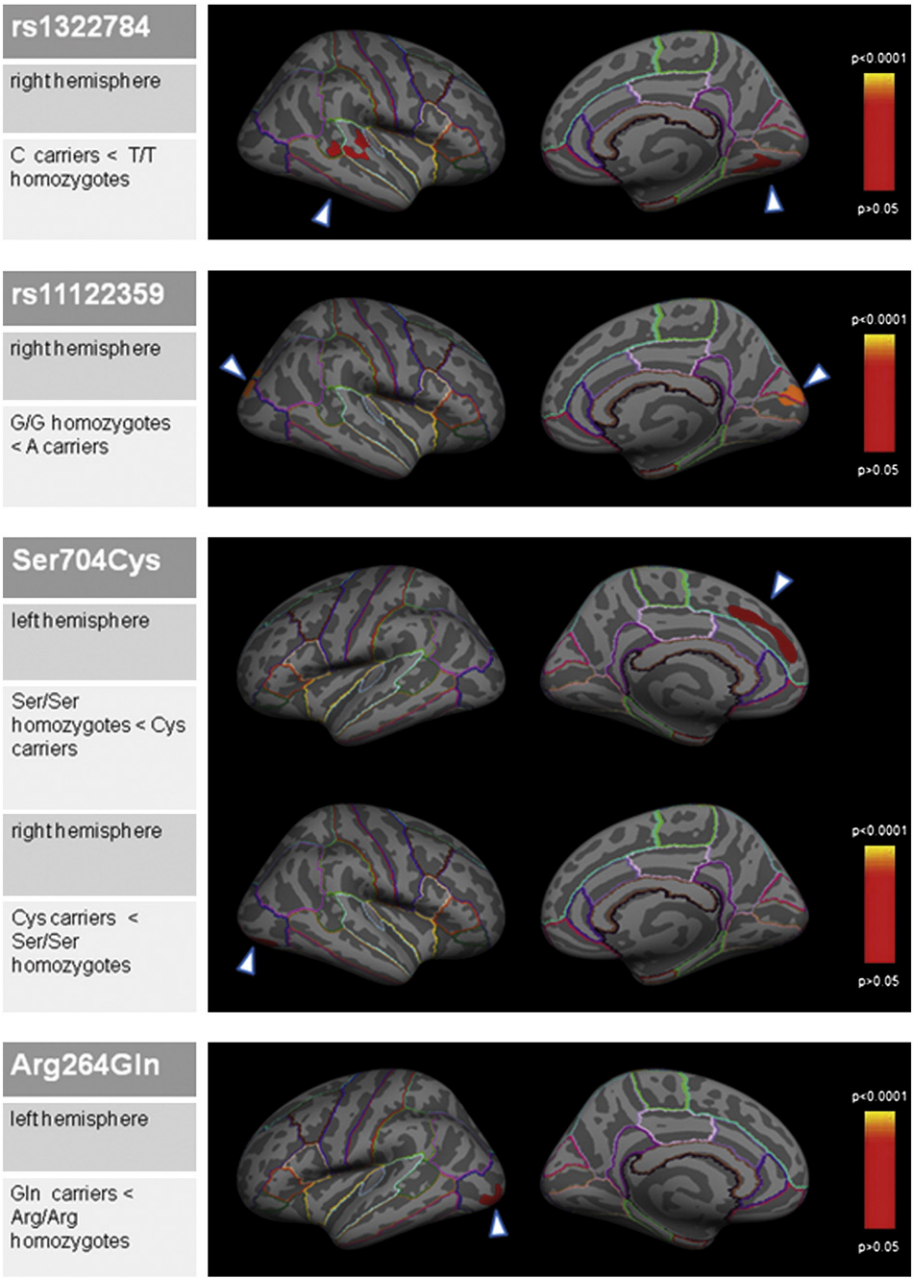

Fig. 2. Cortical statistical maps illustrating regions of genotype effect on cortical thickness for the other four SNPs of DISC after Monte-Carlo-simulation using a VWT of p = 0.05. These maps are shown on the inflated surface of the standard average subject, allowing visualization of data across the entire cortical surface without interference from cortical folding. The CWP-values are represented according to the color code.

Table 3
Regression analyses predicting left and right hippocampus volume covarying for age, gender, intracranial volume and acquisition site.

SNP	Left hippocampus			Right hippocampus		
	Standardized coefficient	T-test	P-value	Standardized coefficient	T-test	P-value
rs1322784	0.072	0.817	0.416	−0.045	−0.554	0.581
rs11122359	−0.156	−1.843	0.069	−0.049	−0.619	0.537
Leu607Phe	−0.059	−0.666	0.507	−0.051	−0.651	0.516
Ser704Cys	0.033	0.372	0.710	0.034	0.413	0.681
Arg264Gln	−0.019	−0.22	0.827	−0.040	−0.481	0.632

Kim et al., 2003; Tan et al., 2007; Zhou et al., 2007). Several recent fMRI studies on functional connectivity during working memory provide support for this "disconnection hypothesis". For example, prefronto-parietal coupling was found to be reduced in schizophrenia patients and the magnitude of prefronto-parietal coupling correlated positively with better working memory performance but negatively with overall symptom severity (Henseler et al., 2009). Another study using the same working memory task and a subset of the same subjects of our own study, found evidence for an altered task-correlated network comprising the left DLPFC and inferior parietal lobules in schizophrenia patients (Kim et al., 2009a).

Our own findings of increased prefrontal activity in DISC1 Phe carriers, given the same working memory performance, can be interpreted as cortical inefficiency, i.e. risk allele carriers need to recruit greater neural resources to perform the same task (Callicott et al., 2000;

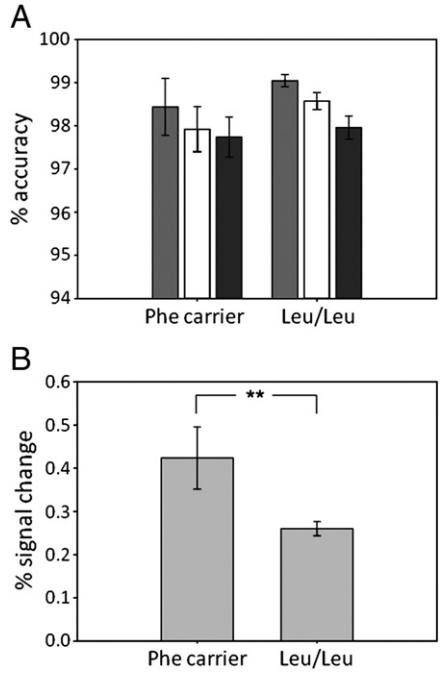

Fig. 3. (A) Performance (given as % accuracy) during the SIRP working memory task at different levels of difficulty (load 1 = gray bars, load 3 = white bars and load 5 = anthracite bars) and (B) increase in neural activity (signal change) with increasing working memory load in the left DLPFC. Error bars represent ±1 standard error.

Kim et al., 2009a; Manoach et al., 1999; Potkin et al., 2009a; Thermenos et al., 2005). Based on findings in non-affected siblings of patients with schizophrenia abnormal working memory performance and working memory related prefrontal inefficiency might reflect an expression of genetic liability to schizophrenia and be itself a potential endophenotype (Glahn et al., 2003; Gur et al., 2007; Horan et al., 2008; MacDonald et al., 2009; Meda et al., 2008; Park et al., 1995; Tan et al., 2007; Whitfield-Gabrieli et al., 2009). One of the first genome wide association study with a brain based quantitative trait marker in schizophrenia used left DLPFC load-dependent signal change as an outcome variable (Potkin et al., 2009b). In line with that, previous behavioral studies found relationships between DISC1 variants and working memory deficits in patients with schizophrenia and their unaffected relatives (Burdick et al., 2005; Hennah et al., 2005). In addition, mutant mice carrying a truncating lesion in the endogenous DISC1 orthologue showed alterations in neuronal architecture and a selective impairment in working memory (Koike et al., 2006; Kvajo et al., 2008).

Previous fMRI studies in healthy humans have focused on the effects of the Ser704Cys polymorphism. Two studies investigated hippocampal function during working memory and episodic memory using an ROI-based approach. However the findings were somewhat contradictory (Callicott et al., 2005; Di Giorgio et al., 2008). In the first study Ser homozygotes showed an uncharacteristic increase in bilateral hippocampal activation during working memory encoding and retrieval compared with Cys carriers but decreased activation in bilateral hippocampus during episodic memory encoding (Callicott et al., 2005). The second study reported that Ser homozygotes had greater neural responses in bilateral hippocampus during episodic memory encoding (Di Giorgio et al., 2008). A voxel-wise analysis of the effects of the Ser704Cys polymorphism on brain activity during a verbal fluency task demonstrated greater activation for the group of Ser homozygotes in the dorsolateral prefrontal cortex (Prata et al., 2008). The heterogeneity of these findings may be explained by the usage of different tasks which might recruit distinct neuronal circuitry. If "abnormality" is defined as any difference between the group with a risk allele and those without it these data also support an important role of DISC1 for brain functions that are impaired in patients with schizophrenia.

The present findings must be interpreted within the context of the limitations of the study. First, it is likely that cortical thickness is influenced by additional gene variants, which have not been studied, as well as by unidentified and more complex haplotypes and gene–gene interactions. Because the majority of SNPs in this study were not in strong linkage disequilibrium, we characterized only one simple haplotype. Regardless of the eventual complexity of the risk haplotypes, the intermediate biologic phenotype data in this study strongly implicate DISC1 allelic variation in the determination of regional cortical thickness, which has been reliably implicated in the pathogenesis of schizophrenia. Second, it is common practice to analyze the effects of genetic risk variants in healthy controls to avoid potential confounders related to illness. The use of antipsychotics, increased prevalence of smoking, early institutionalization and possibly even the loss of social status and learning opportunities have all been suggested to lead to subtle alterations of subcortical and cortical brain structures in patients which might obscure the effects of gene variants which are involved in brain development (Draganski and May, 2008; Navari and Dazzan, 2009; Scherk and Falkai, 2006; Tomelleri et al., 2009; Tregellas et al., 2007). In addition, the effect of risk genes in patients may vary given the presence of other positively or negatively modifying genetic risk variants (McIntosh et al., 2007). To resolve at least some of these issues future studies should test DISC1 risk variants in antipsychotic-naïve patients and unaffected relatives. Third, DISC1 variants have also been implicated in mood disorders (Chubb et al., 2008). Although reduced cortical thickness and working memory-related prefrontal activity are acknowledged intermediate phenotypes for schizophrenia we cannot exclude that the present findings also apply to other psychiatric disorders.

In summary, converging evidence from structural and functional brain imaging data suggest an important role of DISC1 variants on intermediate phenotypes of schizophrenia. The Phe607 allele was associated with reduced cortical thickness in the left supramarginal gyrus and the same allele was related to reduced neural efficiency during a working memory task. Our findings provide support for a neurodevelopmental model of schizophrenia.

Financial disclosures

In the last two years, Dr. Ho has received grant support from NIH (MH068380), NARSAD and Ortho-McNeil Janssen Scientific Affairs. Dr. Heinz received unrestricted grants and speaker honoraria from BMS, Lilly, Janssen-Cilag, Astra-Zeneca and Servier. All other authors declare that there are no conflicts of interest in relation to the subject of this study.

Acknowledgments

This work was supported by NIH/NCRRP41RR14075, Department of EnergyDE-FG02-99ER62764, MIND Research Network, Morphometry BIRN1U24, RR021382A, Function BIRNU24RR021992-01, NIH. NCRR MO1 RR025758-01, the Deutsche Forschungsgemeinschaft (Research Fellowship to S Ehrlich) and the Biomedical Science Exchange Program (Scholarship to S Brauns).

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.05.058.

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