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DISC1 gene and affective psychopathology: A combined structural and functional MRI study

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ABSTRACT

The gene *Disrupted-In-Schizophrenia-1* (DISC1) has been indicated as a determinant of psychopathology, including affective disorders, and shown to influence prefrontal cortex (PFC) and hippocampus functioning, regions of major interest for affective disorders. We aimed to investigate whether DISC1 differentially modulates brain function during executive and memory processing, and morphology in regions relevant for depression and anxiety disorders (affective disorders). 128 participants, with ($n = 103$) and without (controls; $n = 25$) affective disorders underwent genotyping for Ser704Cys (with Cys-allele considered as risk-allele) and structural and functional (f) Magnetic Resonance Imaging (MRI) during visuospatial planning and emotional episodic memory tasks. For both voxel-based morphometry and fMRI analyses, we investigated the effect of genotype in controls and explored genotypeXdiagnosis interactions. Results are reported at $p < 0.05$ FWE small volume corrected. In controls, Cys-carriers showed smaller bilateral (para)hippocampal volumes compared with Ser-homozygotes, and lower activation in the anterior cingulate cortex (ACC) and dorsolateral PFC during visuospatial planning. In anxiety patients, Cys-carriers showed larger (para)hippocampal volumes and more ACC activation during visuospatial planning. In depressive patients, no effect of genotype was observed and overall, no effect of genotype on episodic memory processing was detected. We demonstrated that Ser704Cys-genotype influences (para)hippocampal structure and functioning the dorsal PFC during executive planning, most prominently in unaffected controls. Results suggest that presence of psychopathology moderates Ser704Cys effects.

1. Introduction

The gene *Disrupted-In-Schizophrenia-1* (DISC1) has been identified in a linkage-study as a risk for several psychiatric disorders (Millar et al., 2000; Blackwood et al., 2001). This gene codes for a protein important for neural growth and synaptic modulation (Morris et al., 2003; Kamiya et al., 2006) and the single nucleotide polymorphisms (SNP) Ser704Cys has shown to influence glia-cell functioning (Eastwood et al., 2010). The Cys-allele of this polymorphism has been associated with depression (Hashimoto et al.,

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2006), although genome wide associations failed to show this association with the depression phenotype (Sullivan et al., 2009; Wray et al., 2012). Nevertheless, genetic variations have shown to be potent in explaining variance on an endophenotypical neurobiological level, an approach that might increase our understanding of the complex linkage of genes and the phenotype of affective disorders, including depression and frequent comorbid anxiety disorders.

DISC1-expression is highest in hippocampal regions and prefrontal cortex (PFC) (Porteous et al., 2006; Chubb et al., 2008), regions that have been linked with impairments in affective disorders during memory (Milne et al., 2011; Fairhall et al., 2010; Werner et al., 2009; Van Tol et al., 2012) and executive functioning (Fitzgerald et al., 2008; Goethals et al., 2005; Van Tol et al., 2011). Therefore, altered hippocampal and PFC function during these processes could serve as promising *endophenotypes* in studying the association between DISC1-genotype and affective disorders. Supportive of this suggestion, in healthy people, the Cys-allele of the Ser704Cys SNP has been associated with less hippocampal activation during working memory (WM) and more hippocampal activation during episodic memory (Callicott et al., 2005), and with less activation of the dorsolateral prefrontal cortex (DLPFC) during both memory (Di Giorgio et al., 2008) and executive functioning (Prata et al., 2008). Moreover, smaller hippocampus (Di Giorgio et al., 2008) and anterior cingulate cortex (ACC) volume (Hashimoto et al., 2006) have been demonstrated in Cys-carriers, whereas larger DLPFC volume has been observed (Brauns et al., 2011; Takahashi et al., 2009). These observations suggest that DISC1-genotype is involved in functioning and structure of hippocampal, ACC and prefrontal regions. However, these associations have been found in separate studies. It has to our knowledge not yet been investigated whether these associations could be replicated within one and the same sample. In addition, whether similar associations are present in patients with affective disorders has not been studied to date.

The primary aim of this study was to investigate the effects of Ser704Cys-genotype on function and structure of the ACC, DLPFC and hippocampus in a single sample showing no psychopathology. We hypothesized that Cys-carriers will show smaller grey matter (GM) volumes and less activation during tasks of spatial WM and episodic memory in these regions. Furthermore, we aimed to explore whether similar associations were present in patients with depression and/or anxiety disorders.

2. Materials and methods

2.1. Participants

Participants were recruited from the large-scale longitudinal multi-site Netherlands Study of Depression and Anxiety (NESDA (Penninx et al., 2008)). The ethical review boards of each participating center (University Medical Center Groningen [UMCG], VU Medical Center [VUMC], and Leiden University Medical Center [LUMC]) gave approval for this study. The study was conducted in accordance with the declaration of Helsinki. All participants provided written informed consent.

Exclusion criteria for all participants for the MRI study were 1) presence or history of a neurological or somatic disorder with possible effects on the central nervous system, 2) general MRI contraindications, 3) dependence or recent abuse (past year) of alcohol or drugs, 4) hypertension and 5) use of other psychotropic medication than SSRIs or infrequent use of benzodiazepines (oxazepam or diazepam, maximum of three times a week and not within 48 h before scanning). An additional exclusion criterion for the control group was a history of any DSM-IV axis-I disorder based on the Composite International Diagnostic Interview (CIDI) – lifetime version 2 (Robins et al., 1988). We included all genotyped participants who completed the full MRI-scanning protocol without technical problems and with sufficient task performance (see for criteria (Van Tol et al., 2012; Van Tol et al., 2011)). Diagnoses were defined based on half-year diagnosis assessed using the CIDI.

We included in total 128 participants: 25 controls, 38 depressed patients (MDD), 28 anxiety patients (panic disorder (PD), social anxiety disorder (SAD) and/or generalized anxiety disorder (GAD); ANX) and 37 patients with comorbid depression-anxiety (CAD). Groups were matched on age, education, and sex. All participants were Caucasian and unrelated to each other.

2.2. Clinical variables

Diagnosis was confirmed with the Composite International Diagnostic Interview (CIDI) – lifetime version 2 (Robins et al., 1988). To assess depression and anxiety symptom severity at moment of scanning, the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Beck Anxiety Inventory (BAI) (Beck et al., 1988) was assessed. These measures have good psychometric properties (Beck et al., 1988; Carmody et al., 2006; Bernstein et al., 2010).

2.3. Genotyping

Genotyping was performed in the context of the genome wide association (GWA) study of the Genetic Association Information Network (GAIN) (Sullivan et al., 2009). Perlegen Sciences (Mountain View, CA, USA) performed all genotyping according to standard operating procedures. High-density oligonucleotide arrays were used yielding 599,164 SNPs. These arrays included the SNP rs821616 (Ser704Cys), a T to A base substitution, leading to a serine to cysteine substitution. All groups were in Hardy–Weinberg equilibrium (HWE, [Cys/Cys:Cys/Ser:Ser/Ser] controls 0:14:11 [$\chi^2(1) = 3.78$, $p = 0.05$], MDD 1:19:18 [$\chi^2(1) = 2.38$, p=0.12], CAD 3:20:14 [$\chi^2(1) = 0.26$, $p = 0.26$], ANX 2:14:12 [$\chi^2(1) = 0.60$, $p = 0.44$]). Groups did not differ in genotype distribution ($\chi^2(6) = 3.36$, $p = 0.76$). We compared Cys-carriers (Cys/Cys- and Cys/Ser-genotypes) with Ser-homozygotes, based on the small amount of Cys-homozygotes and in agreement with the literature (Hashimoto et al., 2006; Callicott et al., 2005; Di Giorgio et al., 2008; Prata et al., 2008; Brauns et al., 2011; Takahashi et al., 2009).

2.4. Image acquisition parameters

All participants were scanned using a Philips 3T MR-scanner located at each site. A SENSE-8 channel head coil was used for radio frequency transmission and reception in Groningen and Leiden. In Amsterdam, a SENSE-6 channel head coil was used. For each subject, a series of echo planar imaging (EPI) volumes were obtained, entailing a T2*weighted gradient echo sequence using axial whole brain acquisition, with an interleaved slice acquisition order and with the following settings for Groningen: repetition time (TR) = 2300 ms; echo time (TE) = 28.0 ms; flip angle of 90°; 39 slices per EPI volume; matrix size: 64 × 64; in-plane resolution of 3 × 3 mm; slice thickness 3 mm and no gap. In Amsterdam and Leiden the following settings were used: TE 30 ms; 35 slices; matrix size: 96 × 96 voxels; in-plane resolution: 2.29 × 2.29 mm slice thickness. All images were acquired parallel to the anterior–posterior commissure plane. In addition, a T1-weighted anatomical MRI was made (TR = 9 ms, TE = 3.5 ms, matrix size 256 × 256, voxel size: 1 × 1 × 1 mm, 170 slices).

2.5. Task paradigms

2.5.1. Memory processing

The task (for a full description see (Van Tol et al., 2012; Daselaar et al., 2003)) consisted of an implicit word encoding- and recognition phase. During the encoding phase, participants were asked to classify negative, positive and neutral words (40 each) according to their valence (button press). In addition, 40 baseline trials were presented, which consisted of the words "left", "middle" or "right" (in Dutch), indicating which button to press. Words were presented pseudo-randomized.

After a retention interval of ten minutes during which the T1-weighted anatomical scan was made, old encoding target words (120), new distracter words (120; matched on valence) and 40 baselines were presented pseudo-randomized and participants had to indicate whether they had seen the words previously, probably had seen it, or had not seen it before.

The task was self-paced, but with a maximum presentation duration of five seconds.

2.5.2. Spatial working memory

The Tower of London (ToL) task involves visuospatial planning with varying levels of difficulty that relies on the fronto-parietal executive system (Welsh et al., 1999). The task was designed as described by Van Tol et al. (2011); Van den Heuvel et al. (2003). On the screen two pictures were shown with colored balls on rods, representing two configurations, one start and one goal (Fig. 1). In the task condition, participants had to count the number of steps (ranging from one to five) needed to reach the goal configuration. In the control condition, instructions were to work out the number of blue and yellow balls. We used a pseudo-randomized, self-paced design with maximal presentation duration of 60 seconds for each trial.

Accuracy and response times (RTs) were registered for both tasks.

2.6. Statistical analyses

2.6.1. Clinical, demographic and behavioral data

Group effects on clinical, demographic, and behavioral data were analyzed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Chi–Square tests and analyses of variance (ANOVA) were used to analyze group differences.

For the memory task, the proportion correct recognitions were analyzed with repeated-measures ANCOVA with valence as within-subject variable and diagnosis and genotype as between-subject variables. Age and education were entered as covariates of no interest. This was repeated for the RTs during encoding on the subsequently remembered trials and the RTs to correctly recognized words during recognition.

For the ToL-task, accuracy and RTs were analyzed by means of separate repeated-measures ANCOVAs, using the proportion correct scores and mean RTs per trial type as dependent factors, and psychopathology and genotype as between-subject factors. Age and education were entered as covariates. For *post-hoc* contrasts, we chose a repeated procedure to compare the more difficult step with one step easier (e.g. step5 vs. step4).

For both the memory and ToL-task we tested for a possible confounding effect of selective serotonin reuptake inhibitor (SSRI) use by means of a repeated-measures ANOVA with SSRI-use as between-subject variable and the behavioral measurement as within-subject variable. We chose to test for this possible confounder *post-hoc*, because of the small number of participants in some of the groups.

2.6.2. Preprocessing and model for structural imaging

Structural data were analyzed using voxel-based morphometry (VBM), following diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL (Ashburner. 2007)) using SPM5. Preprocessing of VBM-DARTEL on these data has been described previously (Van Tol et al., 2010). Briefly, we applied the DARTEL approach for registration, normalization, and modulation after unified segmentation of the manually reoriented T1-images and smoothed the resulting grey matter (GM) images using an 8-mm FWHM Gaussian kernel.

A 2 (genotype) by 4 (diagnosis) ANOVA was built with the total brain volume (sum of gray and white matter, demeaned for the group) as covariate of no interest. Voxel-wise comparisons were masked with an explicit optimal threshold GM-mask created using the Masking toolbox (Ridgway et al., 2009).

2.6.3. Preprocessing and models for functional imaging

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping (SPM5; http://www.fil.ion.ucl.ac.uk/

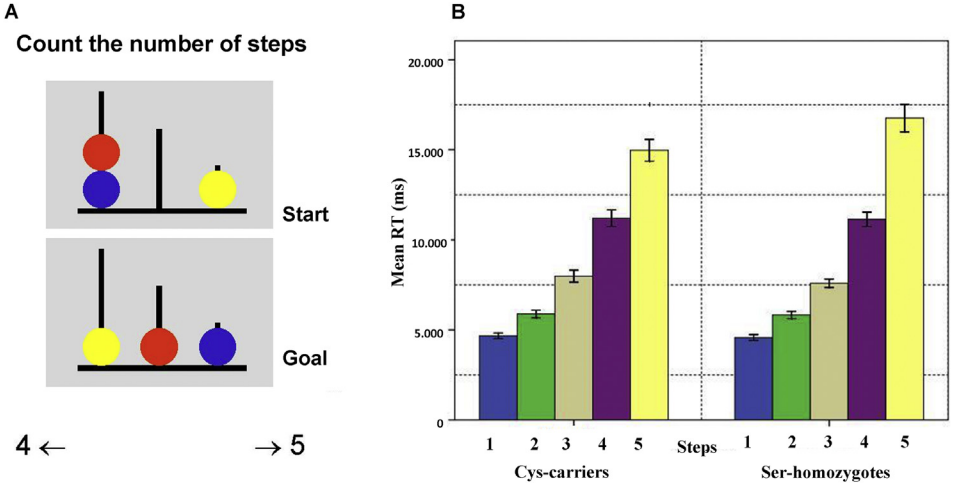

Fig. 1. Tower of London task and genotype effects on response times. A.) On the screen two pictures were shown with colored balls on rods, representing two configurations, one starting configuration and one goal configuration. Participants had to count the number of steps (ranging from one to five) needed to reach the target configuration. We used a pseudorandomized, self-paced design with maximal response duration of 60 seconds for each trial. Accuracy and response times (RTs) were measured. B.) A genotype by task difficulty effect was observed on RTs ($F(1.7196) = 3.51$, $p = 0.04$): *post-hoc* tests showed that Ser-homozygotes had a larger increase in RT from step 4 to step 5 than Cys-carriers ($p = 0.03$). Error bars represent one standard error. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

spm/) implemented in Matlab 7.1.0 (The MathWorks Inc.). Preprocessing included slice-time correction, realignment, registration of the T1-scan to the mean EPI, warping to MNI-space as defined by the T1-template, reslicing to 3 × 3 × 3 mm voxels and spatial smoothing using an 8-mm Full Width at Half Maximum (FWHM) Gaussian kernel.

Complete modeling details for the memory task are described in the supplement. Analysis of the encoding phase was restricted to correctly recognized words in the subsequent recognition phase (successfully encoded words). Contrasts were made for '*encoding_positive* > *encoding_neutral*' and '*encoding_negative* > *encoding_neutral*' Also for the recognition phase analyses were restricted to correct trials and the contrasts '*recognition_positive* > *recognition_neutral*', and '*recognition_negative* > *recognition_neutral*', were calculated following the summary statistics approach. On second level, a full-factorial 2 (genotype) by 4 (diagnosis) by 2 (valence, as non-independent factor) ANOVA was built for the encoding and recognition part separately.

For the ToL-task, regressors were constructed by convolving each event-related stimulus function (baseline, 1–5 step trials) with a canonical hemodynamic response function and modulated using RTs. In addition, error and no-response trials were included as a regressor of no interest. Contrast images for "*task load*" (with trial types 1–5 having weights [−1.5 −1 −0.5 1 2]) were calculated per subject on a voxel-by-voxel basis (Van Tol et al., 2011). On second level, a 2 (genotype) by 4 (diagnosis) ANOVA was built.

2.6.4. Regions of interest and statistical thresholds

Based on literature (see introduction) regarding executive and memory function in affective disorders and effects of DISC1 on neural processing, we selected the following regions of interest (ROIs): anterior cingulate cortex (ACC; BA 32 and 24), bilateral DLPFC (BA 9 and 46), and bilateral parahippocampal areas (hippocampus and parahippocampal gyrus [PHG]) based on the automated anatomical labeling (AAL) atlas (Maldjian et al., 2003) implemented in the Wake Forest University (WFU) pickatlas (http://fmri.wfubmc.edu/cms/software). These labels were used to construct ROIs, which were applied as masks for the small volume corrections.

For all models, we first investigated the effect of genotype in HC, to investigate the effects of the SNP on the healthy brain. These effects were reported at $p < 0.05$, family wise error (FWE) corrected for the spatial extent of the ROI at the voxel level, with an initial voxel-wise threshold of $Z > 3.09$ (equivalent to $p < 0.001$ uncorrected).

We next explored whether the effects seen in HC were also present in patients with a threshold of $p < 0.05$, family wise error (FWE) corrected for the spatial extent of the ROI at the voxel level, with an initial voxel-wise threshold of $Z > 3.09$ (equivalent to $p < 0.001$ uncorrected). In addition, we formally tested for the presence of an interaction between genotype and diagnosis using an F-test at $p < 0.001$, uncorrected.

Effects occurring outside of our predefined ROIs had to meet $p < 0.05$ FWE whole brain corrected at the voxel level, with an initial voxel-wise height threshold of $Z > 3.09$.

The effects of diagnosis in this sample on brain function during visuospatial planning (Van Tol et al., 2011), episodic memory (Van Tol et al., 2012) and regional morphometry (Van Tol et al., 2010) have been reported previously.

To test for the effects of possible confounding variables such as selective serotonin reuptake inhibitor (SSRI) use, education, age, sex, scanning center, symptom severity (measured with MADRS and BAI) and regional volume, the mean voxel signals of significant clusters were calculated using MarsBaR (Brett et al., 2002) and exported to SPSS. We chose to test for these possible confounders *post-hoc*, because of the small number of participants in some of the groups.

3. Results

3.1. Genotype associations on demographic and clinical data

Demographic and clinical data are summarized in Table 1. Diagnostic groups did not differ on genotype distribution, and no effect of genotype or diagnosis was observed on any of the demographic variables (all $p > 0.05$). The diagnostic groups differed from each other on depression and anxiety severity based on respectively MADRS- and BAI-scores.

Table 1
Demographics and clinical variables for Ser704Cys.

A) Divided according to genotype

	Ser/Ser	Cys	Test-value	p
N	55	73		
# Males (%)	19 (34.5)	29 (39.7)	$\chi^2(1) = 0.36$	0.55
Age	36.18 (10.10)	36.93 (9.87)	$t(126) = 0.42$	0.67
Years of education	13.18 (2.70)	12.82 (2.89)	$t(126) = 0.72$	0.47
Scanning site (VUMC/LUMC/UMCG)	15/24/16	23/24/26	$\chi^2(2) = 4.57$	0.48
Diagnosis (HC/MMD/MDD+/ANX)	11/18/14/12	14/20/23/16	$\chi^2(3) = 0.71$	0.87
MADRS scores	11.50 (9.21)	11.94 (9.75)	$t(124) = 0.26$	0.80
BAI scores	9.35 (13.72)	11.93 (10.56)	$t(126) = 1.21$	0.23
# Medication use (%)	12 (21.8)	26 (35.6)	$\chi^2(1) = 2.86$	0.09

B) Divided according to diagnosis

	Controls	MDD only	ANX only	MDD + ANX	Test-value	p
N	25	38	28	37		
# Males (%)	12 (48)	15 (39.5)	8 (28.6)	13 (35.1)	$\chi^2(3) = 2.28$	0.52
Age	39.36 (9.38)	36.63 (9.97)	35.07 (7.84)	35.89 (11.57)	$F(3, 127) = 0.93$	0.43
Years of education	14.12 (2.26)	13.08 (2.84)	12.46 (3.09)	12.49 (2.75)	$F(3, 127) = 2.15$	0.10
Scanning site (VUMC/LUMC/UMCG)	10/10/5	10/13/15	8/10/10	10/15/12	$\chi^2(6) = 3.25$	0.77
# Cys-allele (%)	14 (56)	20 (52.6)	16 (57.1)	23 (62.1)	$\chi^2(3) = 0.71$	0.87
MADRS scores	0.76 (1.56)	12.22 (8.43)	13.14 (8.58)	17.68 (8.05)	$F(3, 125) = 25.95$	<0.001
BAI scores	2.32 (2.93)	5.50 (12.49)	15.68 (11)	18.35 (9.89)	$F(3, 127) = 18.72$	<0.001
# Medication use (%)	–	10 (26.31)	9 (32.14)	19 (51.35)	$\chi^2(2) = 5.42$	0.06

Abbreviations: ANX: anxiety disorder; MDD: Major Depressive Disorder; VUMC: VU Medical Center; UMCG: University Medical Center Groningen; HC: healthy controls; MADRS: Montgomery-Asberg rating scale; BAI: Beck Anxiety Inventory.

3.2. Effect of Ser704Cys on behavioral data

Regarding memory performance, neither genotype nor genotype by diagnosis interaction affected recognition accuracy (all $F < 2.19$, $p > 0.13$) or RTs (All $F < 2.40$, $p > 0.07$; Supplement Table 1).

For visuospatial working memory (WM, Tower of London task), a genotype by task load effect was observed on RTs over the whole sample (see for statistics Fig. 1 and Supplement Table 1), indicating a larger increase in RT from 4-steps to 5-steps in Ser-homozygotes than Cys-carriers. Overall, no effect of diagnosis or interaction of genotype and diagnosis was present on RTs ($F < 0.38$, $p > 0.77$). No effects of genotype, diagnosis, nor interaction between genotype and diagnosis were observed on planning accuracy ($F < 1.37$, $p > 0.26$).

SSRI-use did not have an effect on proportion correct or RT during both the memory- and the ToL-task.

3.3. Effect of Ser704Cys on the healthy brain

Differences in regional GM-volume were seen in the bilateral parahippocampal gyrus (PHG) extending to the hippocampus. Cys-carriers showed smaller volumes compared to Ser-homozygotes (see Table 2 for statistics).

There were no effects of Ser704Cys on brain activation during memory encoding or recognition. However, during visuospatial WM, Cys-carriers showed less activation in the right dorsal ACC and right DLPFC compared to Ser-homozygotes (Table 2, Fig. 2).

3.4. Effect of Ser704Cys on the brain of patients with affective disorders

The effect of Ser704Cys genotype on (para)hippocampal volume as seen in HC, was reversely observed within ANX: Cys-carriers showed enlarged volume compared to Ser-homozygotes. In MDD and CAD, there was no effect of genotype on hippocampal volumes. In addition, within ANX, Ser704Cys had also an influence on ACC and DLPFC volume: ANX Cys-carriers had larger volumes compared to Ser-homozygotes. These effects were absent in HC. Formal interactions of genotype and diagnosis on regional GM volumes confirmed the specificity of genotype effects for HC and ANX in the bilateral PHG/hippocampus (left $F = 10.94$; right $F = 9.54$), and for ANX in the ACC ($F = 9.20$), and bilateral DLPFC (left $F = 6.78$; right $F = 9.73$).

Although in HC no effect of Ser704Cys was seen on activation during memory processing, ANX Cys-carriers showed increased right hippocampal activation compared with Ser-homozygotes during encoding of positive words (Table 2). No such effects were observed during encoding of negative words, nor in the other groups. A formal interaction of genotype by diagnosis by valence was observed in the right hippocampus during memory encoding ($F = 6.01$). During recognition, there was no effect of genotype in the patient groups.

During visuospatial WM, within ANX an opposite pattern of genotype was observed. In the dorsal ACC, ANX Cys-carriers showed greater activation than Ser-homozygotes. There was no effect of genotype in MDD and CAD patients. In contrast to HC, in the right DLPFC there was no effect of genotype in patients, whereas in the left DLPFC only in CAD an effect of genotype on activation was seen (i.e. Cys < Ser) and not in controls, MDD, and ANX. These effects were confirmed in a formal interaction between diagnosis and genotype (ACC $F = 8.88$; left DLPFC $F = 6.99$; right DLPFC $F = 7.00$).

Effects were unaffected by age, sex, education, scanning center, medication use, depression/anxiety severity, grey matter volumes or RTs.

4. Discussion

To our knowledge, this is the first study that investigated effects of DISC1-genotype on structure and function during both

Table 2
Genotype effects of Ser704Cys on structural and functional data in our regions of interest.

Region	Side	Direction of effect	MNI coordinates			K[a]	t	P_{FWE}[b]	Cohen's *d*
			x	*y*	*z*				
Ser704Cys in HC									
Structural									
Parahippocampal gyrus/hippocampus	R	Ser/Ser > Cys	28	−1	−30	373	4.32	0.009	0.79
Parahippocampal gyrus/hippocampus	L	Ser/Ser > Cys	−29	−6	−18	245	4.02	0.024	0.73
Tower of London									
Anterior cingulate cortex (dorsal)	R	Ser/Ser > Cys	6	21	39	16	3.81	.042	0.70
Dorsolateral prefrontal cortex	R	Ser/Ser > Cys	33	42	30	20	4.00	0.036	0.73
Ser704Cys in patients									
Structural									
Parahippocampal gyrus/hippocampus	L	ANX: Cys > Ser/Ser	−26	−24	−7	919	4.46	0.005	0.82
Anterior cingulate cortex (rostral)	L	ANX: Cys > Ser/Ser	−11	51	−3	288	5.64	<0.001	1.03
Dorsolateral prefrontal cortex	R	ANX: Cys > Ser/Ser	44	43	31	75	4.32	0.012	0.79
Dorsolateral prefrontal cortex	L	ANX: Cys > Ser/Ser	−41	25	33	161	4.13	0.023	0.76
Memory encoding									
Hippocampus	R	ANX: Cys > Ser/Ser (pos)	24	−39	3	18	4.19	0.014	0.54
Tower of London									
Anterior cingulate cortex (dorsal)	L	ANX: Cys > Ser/Ser	−3	24	39	45	4.13	0.015	0.75
Dorsolateral prefrontal cortex	L	CAD: Ser/Ser > Cys	−48	36	18	33	3.94	0.044	0.72

The *post-hoc* results are shown in this table. Results were regarded significant at $p < 0.05$ FWE corrected for the spatial extent for the region of interest. For the structural data, there was no main effect of genotype on total grey matter (GM) volume ($F(1,117) = 0.13$, $p = 0.72$) observed, but a genotype by diagnosis interaction was present for total GM volume ($F(3,117) = 3.58$, $p = 0.02$), corrected for age, sex and medication. *Post-hoc t*-tests showed that only within ANX, Cys-carriers had higher total GM volume compared to Ser-homozygotes ($t = 2.77$, $p = 0.01$), whereas no effect of genotype was observed within controls, MDD, or CAD. For the analysis on regional GM we took into account that genotype subgroups differed on this variable by subtracting the mean GM total volume of the subgroup.
The results for the memory encoding were specific for positive words (pos). The results for memory recognition were independent of diagnostic group or word valence.
ANX = anxiety group; CAD = comorbidity anxiety and depression group.

[a] The number of voxels of the entire clusters at $p < 0.001$ uncorrected.

[b] The *p*-value reported is the peak voxel of the cluster. A threshold was set at $p < 0.05$ family wise error (FWE) voxel-wise corrected for the spatial extent of the region-of-interest (ROI), with the initial voxel-wise height threshold set at $Z > 3$.

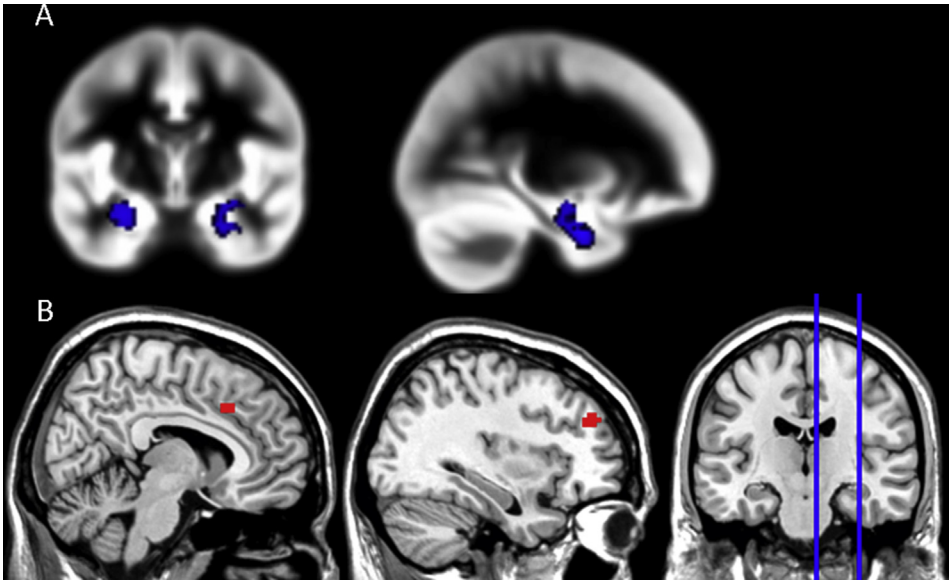

Fig. 2. Effects of Ser704Cys genotype on brain volume (A) and function during ToL (B,C) in healthy participants. A.) Increased parahippocampal volume in Ser-homozygotes compared to Cys-carriers in HC. B.) Increased anterior cingulate cortex (ACC) and right dorsolateral prefrontal cortex (DLPFC) activation in Ser-homozygotes in HC. All depicted at a threshold of $p < 0.001$.

emotional memory and executive functioning in a single sample consisting of participants with and without current affective psychopathology. Consistent with the literature, we found in healthy participants an influence of Ser704Cys on hippocampal and PFC morphology: the Cys-allele was associated with lower volume. In addition, Cys-carriers showed less activation during spatial working memory (WM) in the dorsal ACC, and dorsal PFC. These effects were reversed in patients with an anxiety disorders, whereas there was no effect of genotype in patients with depression. During episodic memory processing, there was no effect of genotype in healthy participants, but there was an association in anxiety patients. This might suggest that presence of psychopathology moderates Ser704Cys effects.

4.1. Effect of Ser704Cys on the healthy brain

In agreement with a previous report (Di Giorgio et al., 2008), we demonstrated that healthy Cys-carriers had smaller parahippocampal gyrus (PHG) and hippocampal volume than healthy Ser-homozygotes. The PHG has an important role in episodic memory (de Curtis and Pare. 2004; Eichenbaum et al., 2007). Additionally, the PHG, together with the hippocampus, is involved in processing of emotional (Drevets et al., 2008; Iidaka et al., 2001) and visuospatial information (de Curtis and Pare. 2004). This Ser704Cys-related difference in PHG and hippocampal volume may thus affect memory, visuospatial and emotion processing abilities, at least within healthy people. Studies in DISC1-mutant mice have shown decreased neurogenesis, neuronal migration and an increase in depressive- and anxiety-like behavior (Clapcote et al., 2007; Haque et al., 2012; Lee et al., 2011). Notably, smaller PHG volumes have been found in anxiety disorders (Massana et al., 2003; Liao et al., 2011) and depression (Abe et al., 2010; Kempton et al., 2011). It has been proposed that volume reductions of hippocampal areas in depression are related to stress and related glucocorticoid levels (Bremner. 2006; Lee et al., 2002; Tata and Anderson. 2010). Based on our results, it could be proposed that reduced hippocampal volume related to carrying the Cys-'risk'-allele might also predispose to vulnerability for these disorders.

During visuospatial WM, healthy Cys-carriers showed less activation in the ACC and DLPFC with increasing planning load compared to healthy Ser-homozygotes. Less DLPFC activation in Cys-carriers has been shown for other executive processes as well (Prata et al., 2008), but this is the first study that showed genotype-related variation in DLPFC activation specifically during visuospatial WM. Decreased functionality of the DLPFC has been suggested to lead to a reduction in control over the emotional state and less flexibility in diverging attention (Phillips et al., 2003), which may increase vulnerability for developing an affective disorder. Indeed, affective disorders have been associated with less DLPFC activation during executive functioning (Goethals et al., 2005; Elliott et al., 1997), although not consistently (Fitzgerald et al., 2008; Van Tol et al., 2011).

In contrast to previous studies (Callicott et al., 2005; Di Giorgio et al., 2008), we did not find an influence of Ser704Cys on hippocampal activation during episodic memory in healthy participants. This is to our knowledge the first study investigating the influence of Ser704Cys on brain activation on different tasks within the same sample. Therefore, based on our findings it might be suggested that DISC1-genotype has a larger effect on WM than on memory functioning. Another possible explanation could be that the memory task used in this study relied largely on emotional processing and the effects of DISC1 have been suggested to be associated with more cognitive functioning (Porteous et al., 2006).

4.2. Effect of Ser704Cys on the brain of patients with an affective disorder

A noteworthy finding in our study was that presence of an affective disorder moderated the effect of Ser704Cys on brain structure and function. Previous neuroimaging studies have also shown moderating effects of psychiatric diagnoses on the influence of genotype on the brain (Mechelli et al., 2008; Prata et al., 2009, 2011). This could be related to other factors influencing brain physiology, including SSRI use, other genes (e.g. brain-derived neurotrophic factor [BDNF](Molendijk et al., 2012), depressive state (Van Tol et al., 2011), or epigenetic influences (Mechelli et al., 2008)). However, previous studies by our group have shown no

effects of SSRI use in this sample on brain morphology or activation during visuospatial or memory processing (Van Tol et al., 2012; Van Tol et al., 2011; Van Tol et al., 2010). Moreover, evidence from animal studies has shown that SSRI use might only affect neurogenesis in youth, not in adulthood (Couillard-Despres et al., 2009; Navailles et al., 2008). In addition, we controlled for SSRI use and depressive state in the current analyses. A recent animal study has shown that DISC1-mutations are leading to anxiety-like behavior only in the context of stress (Haque et al., 2012), which could suggest epigenetic influences. Moreover, for other genes it has also been demonstrated in humans that depressed patients could be distinguished from healthy people based on methylation profile (Dempster et al., 2011; Fuchikami et al., 2011). Future research should test whether stress might influence DISC1 expression via epigenetic influences.

4.3. Strengths and limitations

To our knowledge, this is the first study investigating the effect of Ser704Cys on brain activation during multiple tasks and on brain structure in participants both with and without depression and/or psychopathology. Despite this strength, some limitations have to be taken into account. First, the subgroups had a relatively small sample size, although with expected genotype proportions. We chose to only include participants who completed both tasks and had high-quality structural data in order to end up with the same sample for the three analyses. This approach was chosen to allow proper comparisons of genetic findings between the different tasks and to exclude the possible differences attributed to a different sample. The relatively small sample size could have influenced the unexpectedly large genotype differences in the anxiety group on regional volume differences. Therefore, caution must be taken in interpreting these results. However, the associations for genotype were very consistent within controls, which bolsters confidence that reliable conclusions regarding a differential genotype effect related to diagnosis can be reached. Second, there were many variables in our sample that could have been confounding factors (e.g. medication use, scanner site). For all identified effects, we have tested for a possible influence of these confounding factors. Despite not finding any influence of these possible confounders, such effects cannot be fully discarded. Third, the DISC1-gene is a complex because there are haplotypes on this gene, including the Ser704Cys SNP, influencing brain structure and activation during memory and executive processing (Callicott et al., 2005; Palo et al., 2007). In addition, DISC1 interacts with other proteins and therefore other genes influence the effects of the DISC1-gene on cognitive functioning (Duff et al., 2013; Rampino et al., 2014). These effects could pose challenges to accurately model the effect of the Ser704Cys SNP.

4.4. Conclusion

In conclusion, we show that DISC1 moderates regional brain volumes in paralimbic structures crucial for emotional encoding and activation in dorsal frontal structures crucial for executive functioning, partially dependent on affective psychopathology. Our results indicate the Cys-allele of the Ser704Cys SNP influences endophenotypes relevant for affective disorders, although overt psychopathology may affect this influence. Replication of these findings is needed.

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Contributors

NvdW, BP, MvB, DV and AA: conception and design of the study. EO, MJvT and SW: acquisition of the data. EO and MJvT performed the analyses, supervised by NvdW, DV and AA. EO, MJvT, RK, NvdW, DV and AA: interpretation of the data. EO drafted the article and all authors revised the article critically for important intellectual content and gave approval of this version to be published.

Conflict of interest

Esther Opmeer, Marie-José van Tol, Rudie Kortekaas, Saskia Woudstra, Mark van Buchem, Brenda Penninx, Dick Veltman and André Aleman declare no conflict of interest. Nic van der Wee received speaking fees from Eli Lilly and Wyeth; and served on advisory panels of Eli Lilly, Pfizer, Wyeth and Servier.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.11.014.

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