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The effects of *CACNA1C* gene polymorphism on prefrontal cortex in both schizophrenia patients and healthy controls

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ABSTRACT

CACNA1C gene polymorphism rs2007044 has been reported to be associated with schizophrenia, but its underlying brain mechanism is not clear. First, we conducted an exploratory functional magnetic resonance imaging (fMRI) study using an N-BACK task and a Stroop task in 194 subjects (55 schizophrenia patients and 139 healthy controls). Our whole brain analysis found that the risk allele was associated with reduced activation of the left inferior frontal gyrus (IFG) during the Stroop task (cluster size = 390 voxels, $P < 0.05$ TFCE-FWE corrected; peak MNI coordinates: x = −57, y = −6, z = 30). We also conducted a functional near-infrared spectroscopy (fNIRS) study using the same Stroop task in an independent sample of 126 healthy controls to validate the fMRI finding. Our repeated-measures ANCOVA on the six channels (20, 27, 33, 34, 40 and 46) within the left IFG also found significant result. The polymorphism rs2007044 showed significant effect on the oxy-Hb data ($F = 5.072$, $P = 0.026$) and showed significant interaction effect with channels on the deoxy-Hb data ($F = 2.841$, $P = 0.015$). Taken together, results of this study suggested that rs2007044 could affect the activation of the left IFG, which was a possible brain mechanism underlying the association between *CACNA1C* gene polymorphism and schizophrenia.

1. Introduction

Schizophrenia is a highly heritable mental disorder with an estimated heritability at about 80% (Sullivan et al., 2003), however, its underlying genetic pathways are largely unknown. One gene that codes for the Ca_v 1.2 voltage-dependent L-type calcium channel alpha 1C subunit (*CACNA1C*, 12p13.3) has been strongly suggested to play an important role in the etiology of schizophrenia. Ca_v 1.2 is the predominant (about 90%) calcium channel in the brain (Hell et al., 1993; Sinnegger-Brauns et al., 2009; Striessnig et al., 2014) and is of vital importance to intracellular signaling pathway activity, gene transcription, mRNA degradation, truncated protein, synaptic plasticity, and neuronal development (Bhat et al., 2012; Moosmang et al., 2005; Striessnig et al., 2014; Wheeler et al., 2012; Zamponi et al., 2015).

The evidence for an association between *CACNA1C* and schizophrenia has mainly come from genome wide association studies (GWAS) (Cross-Disorder Group of the Psychiatric Genomics, 2013; Hamshere et al., 2013; Ripke et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study, 2011). These studies found that multiple polymorphisms in intronic 3 of *CACNA1C* (including rs1006737, rs4765905 and rs1024582) in the same linkage disequilibrium block were significantly associated with schizophrenia. Among them, rs1006737 was the most commonly reported. Studies of Caucasian subjects have demonstrated that the risk allele of rs1006737 is associated with increased expression of mRNA (Bigos et al., 2010), decreased gray matter volume (Franke et al., 2010), and altered function of multiple brain regions (Bigos et al., 2010; Erk et al., 2014; Erk et al., 2010; Krug et al., 2010; Krug et al., 2014; Paulus et al., 2014; Thimm et al., 2011). However, because of the low allelic frequency of this polymorphism's minor allele in

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Han Chinese (MAF = 0.023, as compared to 0.304 in Caucasians), it is unlikely for this SNP to play a major role in schizophrenia among Han Chinese (Park et al., 2011).

Recently, in its GWAS of about 36,989 cases and 113,075 controls, Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC, 2014) identified another *CACNA1C* polymorphism (rs2007044, A/G) as the fourth (the *P*-value was 2.63e-17, the minor G allele was the risk allele) most significant hit out of 128 that met genome-wide significance level. In the same year, Zheng et al. (2014) also reported a significant association between rs2007044 and schizophrenia in a Han Chinese sample. The polymorphism rs2007044 is in the same linkage disequilibrium block as rs1006737, but the former shows less ethnic variation in allele frequencies.

However, the function of rs2007044 has been rarely studied. The only evidence was supplied by Cosgrove et al. (2017). They found significant association between the risk allele of the same SNP and poor working memory at behavioral level. Their followed fMRI study of working memory in 84 healthy volunteers could not find significant genotype effect at regional brain activation however found significant association between the risk allele and decreased functional connectivity of the right dorsal lateral prefrontal cortex. We also aimed to test the neural mechanism of rs2007044. In this study, we first did a functional magnetic resonance imaging (fMRI) study in 194 subjects (55 schizophrenia patients and 139 healthy controls) using a Stroop task in addition to an N-BACK task (to measure working memory). To validate this finding, we conducted a functional near-infrared spectroscopy (fNIRS) study in an independent sample of 126 healthy controls. This strategy of using fNIRS data to validate fMRI results was supported by previous fNIRS-fMRI studies that have showed high correlations between signals in fNIRS and fMRI measurements (Cui et al., 2011). Because schizophrenia have showed reduced activation in prefrontal cortex according to a meta-analysis of 41 fMRI studies of executive function (including N-BACK, Stroop, AX-CPT, etc.) (Minzenberg et al., 2009). It is possible that schizophrenia risk factors such as *CACNA1C* gene polymorphism at rs2007044 would affect the activities of the prefrontal cortex when subjects were completing cognitive tasks. We then hypothesized that the risk allele (G) would be associated with reduced activation of the prefrontal cortex, which may serve as a neuro-mechanism of the *CACNA1C* gene in the pathophysiology of schizophrenia.

2. Materials and methods

The protocol of the study was reviewed and approved by the Institutional Review Board of the Institute of Cognitive Neuroscience and Learning at Beijing Normal University. All subjects were Han Chinese and gave written informed consent for this study.

2.1. Subjects

Study I (fMRI) included 55 schizophrenia patients and 139 healthy controls, and Study II (fNIRS) included an independent sample of 126 healthy controls. The patient sample for Study I was recruited between August 2008 and December 2015 from the inpatients of the Beijing Anding Hospital. All patients fulfilled the DSM-IV criteria (American Psychiatric Association, 2000) for schizophrenia according to the diagnostic consensus of two experienced psychiatrists based on structured interview (SCID) (First et al., 2002). The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen and Xia, 1983) and Positive Symptoms (SAPS) (Andreasen and Xia, 1984) were used to assess patients' negative and positive symptoms. The mean score of the SANS and SAPS was 20.24 ± 7.40 and 21.21 ± 7.12 respectively. All patients were treated with a stable dose of atypical antipsychotics for >2 weeks. Exclusion criteria for the patients included a history of other psychiatric disorders and severe brain injury (any closed or open injuries that may be related to current symptoms or cognitive functions), current substance abuse, currently having acute psychotic episodes, and failure to cooperate during the cognitive tests. The healthy controls were from the same geographical region as the patients and were interviewed by experienced psychiatrists to screen for any personal or family history of psychiatric disorders. Two schizophrenia patients and ten healthy controls were excluded from the analyses due to their excessive head motion (>3° or 3 mm).

For Study II, all subjects were heathy controls and were recruited by advertisement in Beijing from July 2015 to December 2015. The inclusion and exclusion criterion were the same as Study I. Seven subjects were excluded because of their bad data quality.

It needs to mention that we combined the AG with the GG genotype as the risk allele carriers in the final analysis due to the small number of the GG genotype (for Study I: 4 patients and 14 controls; for Study II: 16 controls). The final sample size included in the analysis was 182 (82 non-risk homozygotes [AA genotype] and 100 risk allele carriers [AG/GG]) for Study I and 119 (53 non-risk homozygotes and 66 risk allele carriers) for Study II. Detailed clinical and demographic information was presented in Tables 1 and 2 for Study I and II respectively.

2.2. Genotyping

Genomic DNA was extracted using the standard method. The SNP rs2007044 was genotyped using Taqman allele-specific assays on the 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, U.S.A.). PCR was performed in a 5 μl reaction volume which included 2.5 μl TaqMan™ Genotyping Master Mix, 0.125 μl TaqMan® SNP Genotyping Assays, 0.125 μl TE and 10 ng DNA. The thermal cycling conditions were 50 °C for 2 min, 95 °C for 10 min, 50 cycles of 92 °C for 15 s, and 60 °C for 1 min. The genotypes were identified using Sequence Detection System (SDS) Version 2.4 software (Applied Biosystems). The sample success rate for this SNP was 100%. The reproducibility of the genotyping was 100% according to a duplicate analysis of 20% of the genotypes.

Table 1
Demographic and clinical factors and cognitive performance by rs2007044 genotype (Study I).

		Mean ± SD		F or χ^2	*P*
		AA	AG/GG		
Age	Controls	26.71 ± 5.44	27.49 ± 5.91	0.61	0.438
	Patients	27.88 ± 7.48	27.14 ± 8.89	0.10	0.748
	Total	27.05 ± 6.08	27.39 ± 6.86	0.12	0.726
Gender (male/female)	Controls	46/12	55/16	0.06	0.800
	Patients	19/5	27/2	2.23	0.136
	Total	65/17	82/18	0.22	0.642
Education	Controls	13.17 ± 3.36	12.71 ± 2.98	0.68	0.411
	Patients	13.08 ± 2.93	12.72 ± 3.26	0.17	0.678
	Total	13.15 ± 3.23	12.72 ± 3.05	0.86	0.356
IQ[b]	Controls	116.59 ± 11.32	112. 75 ± 10.55	3.30	0.072
	Patients	104.25 ± 11.77	107.69 ± 6.71	2.16	0.148
	Total	112.98 ± 12.70	111.28 ± 9.83	0.90	0.345
Stroop - conflict effect[b]	Controls	147.35 ± 84.42	173.06 ± 144.92	1.35	0.248
	Patients	202.17 ± 112.78	209.19 ± 118.92	0.10	0.757
	Total	163.39 ± 96.21	183.54 ± 138.28	1.48	0.226
2-back (accuracy)[b]	Controls	0.90 ± 0.11	0.86 ± 0.17	2.20	0.141
	Patients	0.66 ± 0.24	0.74 ± 0.16	1.33	0.254
	Total	0.84 ± 0.19	0.83 ± 0.18	0.13	0.721
2-back (RT)[b]	Controls	349.86 ± 96.81	366.30 ± 116.80	0.25	0.618
	Patients	461.50 ± 209.88	387.73 ± 186.04	1.30	0.260
	Total	379.45 ± 143.51	372.45 ± 139.47	0.21	0.651
PANSS-positive	Patients	22.27 ± 6.85	20.77 ± 7.41	0.89	0.416
PANSS-negative	Patients	19.73 ± 6.80	20.90 ± 8.12	0.14	0.873
Medication dose (mg/d)[a]	Patients	234.72 ± 256.18	275.20 ± 174.63	0.21	0.811

[a] Chlorpromazine equivalents.
[b] Use age, gender as covariates.

Table 2
Demographic factors and cognitive performance by rs2007044 genotype (Study II).

	Mean ± SD		F or χ2	P
	AA	AG/GG		
Age	26.40 ± 4.70	26.55 ± 4.51	0.03	0.861
Gender (male/female)	39/14	54/12	1.17	0.280
Education	12.31 ± 2.71	11.80 ± 3.14	0.90	0.346
IQ[a]	112.21 ± 11.20	110.24 ± 11.91	0.83	0.366
Stroop - conflict effect[a]	138.78 ± 72.42	140.74 ± 86.72	0.09	0.762

[a] Use age, gender as covariates.

2.3. The N-BACK task (the fMRI study only)

The N-BACK task has been described in our previous studies (Yu et al., 2016; Zhang et al., 2015, 2016). Briefly, the stimulus was a white circle presented randomly at one of the four corners of a gray diamond-shaped square. Subjects made responses according to the current location of the white circle (0-back) or the location of the white circle seen 2 trials earlier (2-back) using a fiber-optic response box with four buttons that were also arranged in a diamond shape. Subjects pressed one of the four buttons to match the target stimulus. The task included two runs. Each run (lasting for 192 s) consisted of 8 blocks, in which the 2-back condition alternated with the 0-back condition. A centrally placed fixation cross was presented for 16 s before each set of 4 blocks of the task. Each block started with a 4 s on-screen instruction (either the number "0" or "2" on the center of screen indicating the type of working memory task to be performed). There were 8 trials in each block. In each trial (lasting for 2 s), the stimuli were presented for 500 ms, followed by a 1.5 s blank. All subjects received training before scan until their accuracy showed no more improvement.

2.4. The Stroop task (both the fMRI and fNIRS studies)

The Stroop task had been described in our previous fMRI studies (Yu et al., 2016; Zhang et al., 2016). Briefly, this task included three words in Chinese (red, green and blue) that were displayed randomly in one of the three colors. The task was presented in an event-related design and was comprised of 120 trials which included 84 congruent trials (the meaning of the color matched its color) and 36 incongruent trials (the meaning of the color did not match its color). Each trial began with a 500 ms fixation cross, followed by the stimulus presented for 1 s and then 2.5 s blank. The subjects were required to press one of the three keys to indicate the color of ink while ignoring the meaning of the color word.

2.5. fMRI data acquisition

All imaging data were acquired at the Brain Imaging Center of Beijing Normal University. Subjects were scanned on a Siemens TIM Trio 3 T scanner (Siemens, Erlangen, Germany) with their head snugly fixed with straps and foam pads to restrict head movement. After training on the task, subjects went into the scanner and were asked to perform the task while being scanned. Task-related functional images were collected axially using echo-planar imaging (EPI) sequence: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field of view (FOV) = 200 × 200 mm^2; matrix size = 64 × 64; axial slices = 31; 4.0 mm slice thickness without gap (i.e. interleaved scan); voxel size = 3.1 × 3.1 × 4.0 mm^3.

2.6. fMRI data preprocessing and data analysis

Data preprocessing was implemented using Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK). Preprocessing included slice timing (only for the Stroop task), realignment (to realign all subsequent images generated in each run of a certain subject to the first image, any subject with >3 mm translation or 3° rotation would be excluded), normalization to Montreal Neurological Institute (MNI) space, resampling to voxel size of 3 × 3 × 3 mm^3, and spatial smoothing with 8 mm full-width at half maximum (FWHM) of the Gaussian smoothing kernel. Contrast image (for Stroop task, incongruent condition vs. the congruent condition; for N-BACK task, 2 back vs. 0 back) for each subject was produced in the first-level analysis. In this analysis, a high-pass filter at 128 s was used to remove noise associated with low-frequency confounds. The resulting images were then entered the group-level analyses.

For the group-level data analyses, full factorial two-way ANCOVA was done using SPM8 to test the genotype effect, the diagnosis effect, and the interaction effect of genotype × diagnosis. In this analysis, genotype (AA vs. AG/GG) and diagnosis (schizophrenia vs. controls) were fixed factors and subjects' age, gender, years of education, and IQ were covariates. The group-level statistic inference was done using the threshold-free cluster enhancement (TFCE) approach (10,000 random permutations) (Smith and Nichols, 2009) with thresholding set at $P < 0.05$ family wise error (FWE) corrected for multiple comparisons. This correction was performed using the TFCE toolbox for SPM (http://dbm.neuro.uni-jena.de/tfce). In addition to the correction for multiple comparisons, we did the followed fNIRS study in an independent sample. Both together would reduce the chance of false positive results greatly.

2.7. fNIRS data acquisition

Subjects were seated comfortably in a silent room with dim lighting. They were instructed to avoid unnecessary body movement such as neck movement, biting, and so on. The optodes were placed on the subjects' head. A plastic stick was used to push aside the hair between the optodes and the scalp.

A 58-channel optical topography system (LABNIRS, Shimadzu Corporation, Kyoto, Japan) was used to record the changes of the optical density. The attenuation of three wavelengths of the light source (780, 805 and 830 nm) were measured with the sampling frequency of 17.5439 Hz. 18 emitter and 17 detector optodes arranged in a 5 × 7 matrix (See Fig. 2A) were placed on the forehead of the subjects. The emitter-detector distance was 3 cm, which would allow brain measures about 2–3 cm beneath the scalp (Okada and Delpy, 2003; Toronov et al., 2001). The detector optode "8" between channels No. 3 and No. 4 was located at Fpz according to the international 10/20 system used for electroencephalography and the midline of the matrix paralleled to the medial line. The locations of all the optodes, channels and several landmarks (Cz, Nz, Iz, and left and right pre-auricular points) were recorded using a three-dimension position measuring system (FASTRAC; Polhemus, Colchester, VT, USA). The location information was then registered to Montreal Neurological Institute (MNI) brain coordinates using near-infrared spectroscopy (NIRS)-statistical parametric mapping (NIRS_SPM) (Jang et al., 2009; Tak et al., 2010; Tak et al., 2011; Ye et al., 2009).

2.8. fNIRS data preprocessing and data analysis

The preprocessing step was done using NIRS_SPM version 3.2. We first converted our raw data of the optical density changes to the concentration changes of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) based on the modified Beer-Lambert-Law (Cope et al., 1988). For both oxy-Hb and deoxy-Hb, DCT-based detrending with cut-off of 128 s was used to remove some low frequency confounders such as probe excursion. Hemodynamic response function (hrf) smoothing was used to remove high frequency confounders such as heart rate. The precoloring method was used to remove the temporal correlation from our fNIRS data (Heilbronner and Munte, 2013; Worsley and Friston, 1995). A general linear model (GLM) was used to

model the hemodynamic response for each trial with our observed data, design matrix of two conditions (i.e. congruent condition and incongruent condition) and the error term convolved in. As a result, betas of the congruent condition (con-β) and the incongruent condition (incon-β) were calculated automatically for each channel of each subject. Afterwards, contrast betas of incon-β minus con-β were calculated manually for each subject and used in group-level data analysis.

Data analyses at group-level were done using SPSS 20.0. Based on the result of our Study I that found main effect of genotype within the left IFG (as shown in Figs. 1A and. 2B), we conducted a ROI analysis. Six channels (20, 27, 33, 34, 40 and 46) surrounding the significant cluster that was found in Study I were selected (See Fig. 2A and B). Oxy-Hb and deoxy-Hb were analyzed separately. A two-way repeated-measures ANCOVA was used to explore the genotype effect, the channel effect and the interaction effect of genotype × channel. In this analysis, channel (20, 27, 33, 34, 40 and 46) was entered as within-subject factor, genotype (AA vs. AG/GG) was entered as between-subject factor, and subjects' age, gender, years of education, and IQ were entered as covariates. Significant genotype main effect or interaction effect of genotype × channel was followed up with simple effect analysis of genotype in each channel respectively. In this simple effect analysis, age, gender, years of education and IQ were also used as covariates.

3. Results

3.1. Study I: The fMRI study

No deviation from Hardy-Weinberg Equilibrium (HWE) was found in patients, controls, or the total sample. The two genotype groups were comparable on demographic factors, clinical factors and cognitive task performance. (All *P*-values > 0.05) (See Table 1).

During the Stroop task, our whole brain analysis found significant main effect of genotype at the left IFG (cluster size = 390 voxels, $P < 0.05$ TFCE-FWE corrected; peak MNI coordinates: x = −57, y = −6, z = 30) (See Fig. 1A). Comparing with the non-risk homozygous (AA), the risk allele carriers (AG/GG) showed decreased activation at this region (See Fig. 1B). Within the same region, we also observed significant main effect of diagnosis (See Fig. S1). Being consistent with previous findings (Dehaene et al., 2003; Krabbendam et al., 2009; Taylor et al., 1997), patients showed reduced activation than healthy controls in many regions, including the left IFG. No significant interaction effect of genotype × diagnosis was found across the whole brain.

By contrast, no significant genotype effect or genotype × diagnosis effect was found for the N-BACK fMRI data. So, the subsequent fNIRS study only did analyses on the Stroop task however not on the N-BACK task.

3.2. Study II: The fNIRS study

The Stroop task performance and all other demographic factors were comparable between the two genotype groups. (All *P*-values > 0.05) (See Table 2).

We did our fNIRS analysis on the oxy-Hb and deoxy-Hb separately within the 6 channels (20, 27, 33, 34, 40 and 46) as shown in Fig. 2A and B. In our repeated-measures ANCOVA on the oxy-Hb data, we found significant main effect of genotype ($F = 5.072$, $P = 0.026$). This effect was mainly driven by the channel 27 ($F = 2.263$, $P = 0.026$) and the channel 40 ($F = 2.365$, $P = 0.020$) according to the simple effect analysis at each channel. Being consistent with our finding in Study I, the risk allele carriers also showed significantly reduced activation at both channels (See Fig. 2C). All other channels (20, 33, 34 and 46) showed similar pattern however the results didn't reach the significant level. As for our analysis on the deoxy-Hb data, although we couldn't find significant main effect of genotype, we found significant interaction effect of genotype × channel ($F = 2.841$, $P = 0.015$). The followed analysis at each channel again found significant genotype effect at the channel 40 ($F = 10.078$, $P = 0.002$) (See Fig. 2 D) with the risk allele carriers showed reduced activation.

4. Discussion

In Study I (fMRI), we did an exploratory study and found a significant association between the risk allele (G) of *CACNA1C* polymorphism (rs2007044) and reduced activation of the left IFG during the Stroop task. This result was replicated in Study II (fNIRS) with an independent sample.

The Stroop task is recommended by Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) as a measure of executive control in schizophrenia (Barch et al., 2009; Carter et al., 2012; Nuechterlein et al., 2008). Using the Stroop task, previous studies have consistently reported that schizophrenia patients are impaired at this task (Hepp et al., 1996; Hu et al., 2015; Perlstein et al., 1998; Westerhausen et al., 2011). fMRI studies (including the current one) have further suggested reduced activation of IFG in schizophrenia patients during the Stroop task (Dehaene et al., 2003; Krabbendam et al., 2009; Taylor et al., 1997). Consistently, this region is thinner (Knochel et al., 2016; Kuperberg et al., 2003; Oertel-Knochel et al., 2013) and shows reduced gray matter density/volume (Bhojraj et al.,

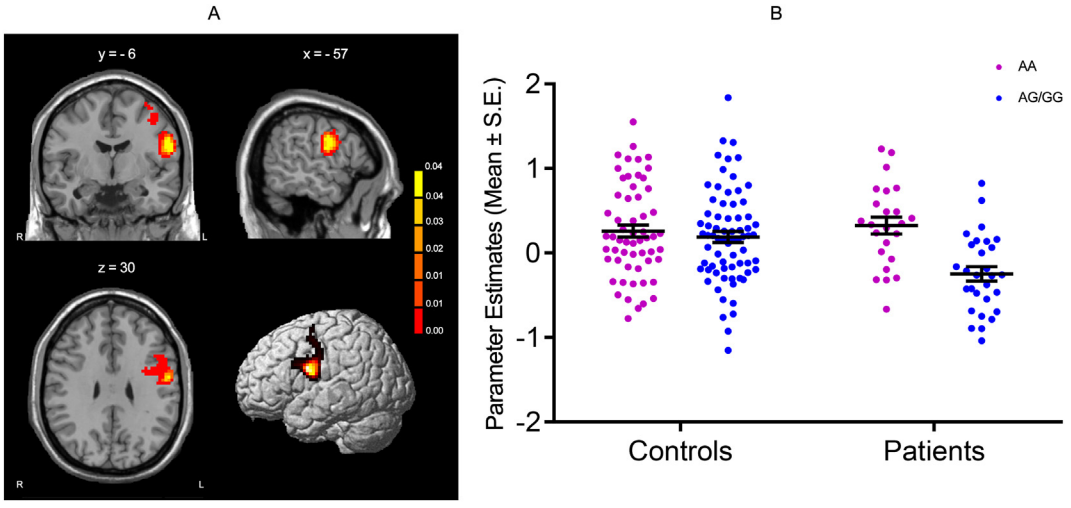

Fig. 1. Genotype effect on activation at the left inferior gyrus (MNI coordinates: x = −57, y = −6, z = 30) during the Stroop task (Study I). The risk allele carriers showed decreased activation at this region.

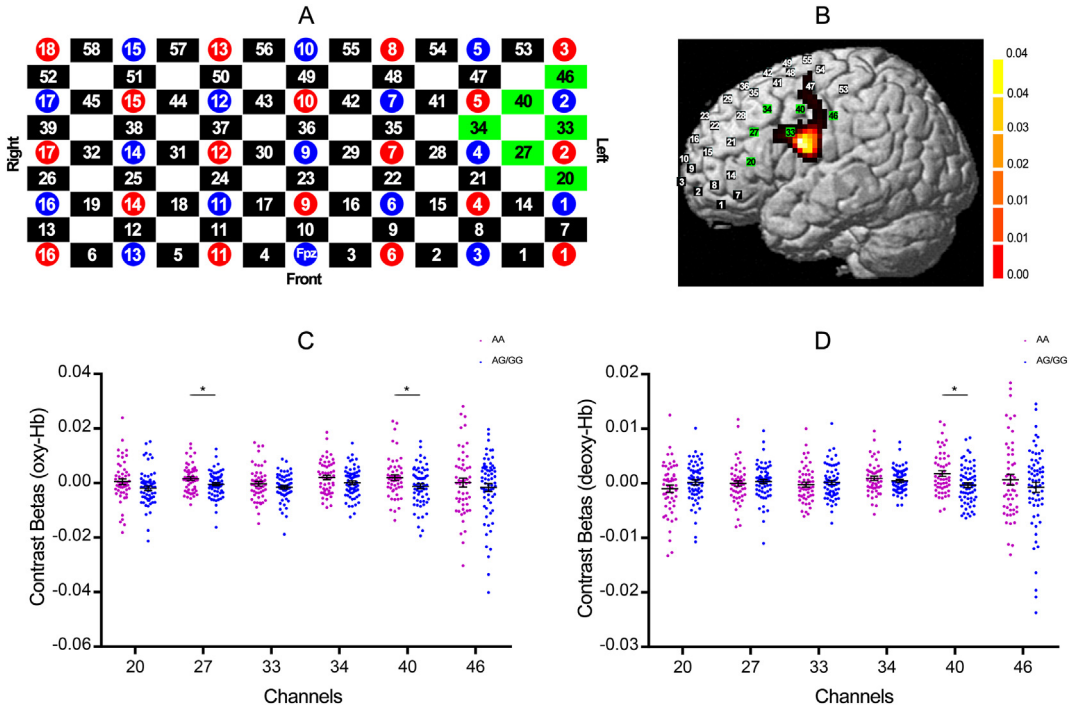

Fig. 2. ROI analysis on the fNIRS data (Study II). Panel A showed the distribution of the optodes and channels: emitter optodes (red circles), detector optodes (blue circles), recording channels (black rectangles), and recording channels that were involved in our ROI analysis (green rectangles). Panel B showed the significant cluster within the left IFG (the same as Fig. 1A) and its position in relation to the fNIRS recording channels. ROI analysis focused on channels 20, 27, 33, 34, 40, and 46 (green rectangles). Panel C showed the contrast Beta of each genotype and each channel in the oxy-Hb analysis. Significant genotype effects were found at channels 27 and 40. Panel D showed the contrast Beta of each genotype and each channel in the deoxy-Hb analysis. Significant genotype effect was again found at the channel 40.

2011; Bora et al., 2011; Chan et al., 2011; Harms et al., 2010) in schizophrenia patients than in healthy controls. The above morphological changes were also found to be associated with impaired executive function (Ehrlich et al., 2012; Guo et al., 2014; Hartberg et al., 2010; Knochel et al., 2016; Oertel-Knochel et al., 2013). Taken together, these results suggest that IFG may contribute to executive control impairment in schizophrenia.

Little is known about neural correlates of *CACNA1C* rs2007044. As far as we know, only two studies explored the neural correlates of rs2007044. One study found that rs2007044 was associated with poor performance on working memory task however showed no significant association with regional brain activation during performance of a working memory task (Cosgrove et al., 2017). Our negative result on the N-BACK task was consistent with it. The other study tested the association between rs2007044 and cortical surface area and thickness across the whole brain however found no significant results (Zheng et al., 2016). It needs to be mentioned that the same study also failed to find any significant differences in surface area and thickness between patients and controls (Zheng et al., 2016). Due to the lack of studies on rs2007044, we have to refer to studies on rs1006737 in Europe sample because the latter is in complete linkage disequilibrium with rs2007044 in Caucasians (the risk G allele of rs2007044 was linked to the risk A allele of rs1006737). Two imaging studies have been conducted with rs1006737. One fMRI study (using the Attention Network Task) found reduced activation at the medial frontal gyrus (MFG) in risk allele carriers (Thimm et al., 2011). MFG has direct fiber and functional connection with IFG (Ford et al., 2010; Sundermann and Pfleiderer, 2012), with the former responsible for conflict detection and the latter for conflict resolution according to the conflict monitoring model (Botvinick et al., 1999; Carter et al., 1998; Garavan et al., 2003; Ullsperger and von Cramon, 2001). The other study was a morphological study showing altered gray matter volume at prefrontal cortex (including IFG) in risk allele carrying healthy controls (Wang et al., 2011).

In terms of neurobiology, the *CACNA1C* gene encodes the Ca_v 1.2 voltage-dependent L-type calcium channel which is located at cell bodies, dendritic spines and shafts and thus can play a critical role in postsynaptic signaling processing (Di Biase et al., 2011; Hall et al., 2013; Hell et al., 1993). Briefly, Ca^{2+} influx via Ca_v 1.2 channel can drive local CaMKII aggregation and trigger activity-dependent gene expression (Ma et al., 2013; Striessnig et al., 2014; Wheeler et al., 2012). Although not specifically about rs2007044, previous studies have suggested that single nucleotide polymorphisms can alter *CACNA1C* gene expression (Gershon et al., 2014) and result in altered neural activity (Yoshimizu et al., 2015). Our results seem to suggest that rs2007044 may contribute to cognitive functions such as executive function through altered *CACNA1C* gene expression. Considering the significant correlations between the executive function impairments and schizophrenia symptoms such as disorganization (Henik and Salo, 2004) and auditory hallucinations (Badcock and Hugdahl, 2014), it is possible that rs2007044 could further contribute to schizophrenia.

The significant genotype effect we found in both fMRI study and fNIRS study was at the left IFG. As suggested by Derrfuss et al.'s studies of the Stroop task (Derrfuss et al., 2005; Derrfuss et al., 2012), the left IFG was activated more frequently than the right IFG. A focal prefrontal damage study also found that the left IFG was significantly related to increased Stroop effect (Tsuchida and Fellows, 2013). The left IFG's role in the Stroop task seems to be related to semantic selection (Kubicki et al., 2003; Thompson-Schill et al., 1998) and verbal conflict resolution (Jonides and Nee, 2006; Jonides et al., 1998; Leung et al., 2000). The importance of verbal processing in the above discussion may also explain why our N-BACK task (a spatial task) did not reveal significant results.

Moreover, our genotype effect in the left IFG was mainly in the posterior part. Muhle-Karbe et al. (2016) isolated the left inferior frontal junction area (at the posterior end of the inferior frontal sulcus) because of this region's specific functions such as selection of task-relevant information. For example, transcranial magnetic stimulation (TMS) administered to the left frontal operculum (posterior part of the IFG) diminished

top-down selective attention (separating relevant information from irrelevant information) (Higo et al., 2011). Similarly, during the Go/NoGo task (a task shares in common with Stroop task that also requires overriding the more automatic however task-inappropriate responses), the NoGo dominant activity was also found at the posterior part of the left inferior frontal sulcus (Konishi et al., 1999). Besides, patients with damage at the left posterior IFG were reported have difficulty when completing the Go/NoGo task (Swick et al., 2008). Finally, we could not find any genotype effect or genotype × diagnosis interaction effect for the N-BACK task, which was consistent with Cosgrove et al. (2017). In addition to the reason we discussed above, it needs to mention that previous functional imaging results of *CACNA1C* gene polymorphism rs1006737 and working memory were mixed. Risk allele carriers were found to show increased activation at the PFC in two studies (Bigos et al., 2010; Krug et al., 2010) but decreased activation at the PFC in a third study (Paulus et al., 2014). It seems that more research is needed to clarify these mixed findings.

In conclusion, using both fMRI data and fNIRS data, this study consistently showed that the risk allele of *CACNA1C* gene polymorphism at rs2007044 was associated with significantly reduced activation of the left IFG. The current neuroimaging genetics study supported a role of *CACNA1C* gene in the etiology of schizophrenia and determined the neuro-mechanism of *CACNA1C* variant such as rs2007044, which will be helpful for the future translation into clinical application such as offering new treatment targets.

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Contributors

Jun Li had full access to all of the data in the study. Jun Li, Qi Dong and Chuansheng Chen designed the study and wrote the protocol. Qiumei Zhang, Jinguo Zhai, Min Chen, Feng Ji, Chuanyue Wang, Yutao Xiang and Hongjie Wu selected the patient sample and evaluated them. Zhifang Zhang, Wan Zhao and Xiongying Chen evaluated the healthy controls. Boqi Du, Xiaoxiang Deng and Dawei Li managed the literature searches and analyses. Zhifang Zhang and Qiumei Zhang undertook the statistical analysis. Zhifang Zhang wrote the first draft of the manuscript and Yanyan Wang made important modifications. All authors contributed to and have approved the final manuscript.

Conflict of interest

There was no conflict of interest in this study.

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References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR). American Psychiatric Association.

Andreasen, N., Xia, M., 1983. . transl. The Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City.

Andreasen, N., Xia, M., 1984. . transl. The Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City.

Badcock, J.C., Hugdahl, K., 2014. A synthesis of evidence on inhibitory control and auditory hallucinations based on the Research Domain Criteria (RDoC) framework. Front. Hum. Neurosci. 8, 180.

Barch, D.M., Braver, T.S., Carter, C.S., Poldrack, R.A., Robbins, T.W., 2009. CNTRICS final task selection: executive control. Schizophr. Bull. 35 (1), 115–135.

Bhat, S., Dao, D.T., Terrillion, C.E., Arad, M., Smith, R.J., Soldatov, N.M., Gould, T.D., 2012. CACNA1C (Cav1.2) in the pathophysiology of psychiatric disease. Prog. Neurobiol. 99 (1), 1–14.

Bhojraj, T.S., Sweeney, J.A., Prasad, K.M., Eack, S.M., Francis, A.N., Miewald, J.M., Montrose, D.M., Keshavan, M.S., 2011. Gray matter loss in young relatives at risk for schizophrenia: relation with prodromal psychopathology. NeuroImage 54 (Suppl. 1), S272–S279.

Bigos, K.L., Mattay, V.S., Callicott, J.H., Straub, R.E., Vakkalanka, R., Kolachana, B., Hyde, T.M., Lipska, B.K., Kleinman, J.E., Weinberger, D.R., 2010. Genetic variation in CACNA1C affects brain circuitries related to mental illness. Arch. Gen. Psychiatry 67 (9), 939–945.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S.J., Yucel, M., Velakoulis, D., Pantelis, C., 2011. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr. Res. 127 (1–3), 46–57.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., Cohen, J.D., 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402 (6758), 179–181.

Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D., Cohen, J.D., 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 280 (5364), 747–749.

Carter, C.S., Minzenberg, M., West, R., MacDonald 3rd, A., 2012. CNTRICS imaging biomarker selections: executive control paradigms. Schizophr. Bull. 38 (1), 34–42.

Chan, R.C., Di, X., McAlonan, G.M., Gong, Q.Y., 2011. Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. Schizophr. Bull. 37 (1), 177–188.

Cope, M., Delpy, D.T., Reynolds, E.O., Wray, S., Wyatt, J., van der Zee, P., 1988. Methods of quantitating cerebral near infrared spectroscopy data. Adv. Exp. Med. Biol. 222, 183–189.

Cosgrove, D., Mothersill, O., Kendall, K., Konte, B., Harold, D., Giegling, I., Hartmann, A., Richards, A., Mantripragada, K., Owen, M.J., O'Donovan, M.C., Gill, M., Rujescu, D., Walters, J., Corvin, A., Morris, D.W., Donohoe, G., 2017. Cognitive characterization of schizophrenia risk variants involved in synaptic transmission: Evidence of CACNA1C's role in working memory. Neuropsychopharmacology 42 (13), 2612–2622.

Cross-Disorder Group of the Psychiatric Genomics, C, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381 (9875), 1371–1379.

Cui, X., Bray, S., Bryant, D.M., Glover, G.H., Reiss, A.L., 2011. A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. NeuroImage 54 (4), 2808–2821.

Dehaene, S., Artiges, E., Naccache, L., Martelli, C., Viard, A., Schurhoff, F., Recasens, C., Martinot, M.L., Leboyer, M., Martinot, J.L., 2003. Conscious and subliminal conflicts in normal subjects and patients with schizophrenia: the role of the anterior cingulate. Proc. Natl. Acad. Sci. U. S. A. 100 (23), 13722–13727.

Derrfuss, J., Brass, M., Neumann, J., von Cramon, D.Y., 2005. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. Hum. Brain Mapp. 25 (1), 22–34.

Derrfuss, J., Vogt, V.L., Fiebach, C.J., von Cramon, D.Y., Tittgemeyer, M., 2012. Functional organization of the left inferior precentral sulcus: dissociating the inferior frontal eye field and the inferior frontal junction. NeuroImage 59 (4), 3829–3837.

Di Biase, V., Tuluc, P., Campiglio, M., Obermair, G.J., Heine, M., Flucher, B.E., 2011. Surface traffic of dendritic CaV1.2 calcium channels in hippocampal neurons. J. Neurosci. 31 (38), 13682–13694.

Ehrlich, S., Brauns, S., Yendiki, A., Ho, B.C., Calhoun, V., Schulz, S.C., Gollub, R.L., Sponheim, S.R., 2012. Associations of cortical thickness and cognition in patients with schizophrenia and healthy controls. Schizophr. Bull. 38 (5), 1050–1062.

Erk, S., Meyer-Lindenberg, A., Schnell, K., Opitz von Boberfeld, C., Esslinger, C., Kirsch, P., Grimm, O., Arnold, C., Haddad, L., Witt, S.H., Cichon, S., Nothen, M.M., Rietschel, M., Walter, H., 2010. Brain function in carriers of a genome-wide supported bipolar disorder variant. Arch. Gen. Psychiatry 67 (8), 803–811.

Erk, S., Meyer-Lindenberg, A., Schmierer, P., Mohnke, S., Grimm, O., Garbusow, M., Haddad, L., Poehland, L., Muhleisen, T.W., Witt, S.H., Tost, H., Kirsch, P., Romanczuk-Seiferth, N., Schott, B.H., Cichon, S., Nothen, M.M., Rietschel, M., Heinz, A., Walter, H., 2014. Hippocampal and frontolimbic function as intermediate phenotype for psychosis: evidence from healthy relatives and a common risk variant in CACNA1C. Biol. Psychiatry 76 (6), 466–475.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., Fei, L.P., Liu, X.H., et al., 2002. . transl. Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Patient Edition (SCID-I/P). Biometrics Research, New York State Psychiatric Institute, New York.

Ford, A., McGregor, K.M., Case, K., Crosson, B., White, K.D., 2010. Structural connectivity of Broca's area and medial frontal cortex. NeuroImage 52 (4), 1230–1237.

Franke, B., Vasquez, A.A., Veltman, J.A., Brunner, H.G., Rijpkema, M., Fernandez, G., 2010. Genetic variation in CACNA1C, a gene associated with bipolar disorder, influences brainstem rather than gray matter volume in healthy individuals. Biol. Psychiatry 68 (6), 586–588.

Garavan, H., Ross, T.J., Kaufman, J., Stein, E.A., 2003. A midline dissociation between error-processing and response-conflict monitoring. NeuroImage 20 (2), 1132–1139.

Gershon, E.S., Grennan, K., Busnello, J., Badner, J.A., Ovsiew, F., Memon, S., Alliey-Rodriguez, N., Cooper, J., Romanos, B., Liu, C., 2014. A rare mutation of CACNA1C in a patient with bipolar disorder, and decreased gene expression associated with a bipolar-associated common SNP of CACNA1C in brain. Mol. Psychiatry 19 (8), 890–894.

Guo, X., Li, J., Wang, J., Fan, X., Hu, M., Shen, Y., Chen, H., Zhao, J., 2014. Hippocampal and orbital inferior frontal gray matter volume abnormalities and cognitive deficit in treatment-naive, first-episode patients with schizophrenia. Schizophr. Res. 152 (2–3), 339–343.

Hall, D.D., Dai, S.P., Tseng, P.Y., Malik, Z., Nguyen, M., Matt, L., Schnizler, K., Shephard, A., Mohapatra, D.P., Tsuruta, F., Dolmetsch, R.E., Christel, C.J., Lee, A., Burette, A., Weinberg, R.J., Hell, J.W., 2013. Competition between alpha-actinin and Ca2+-calmodulin controls surface retention of the L-type Ca2+ channel Ca(v)1.2. Neuron 78 (3), 483–497.

Hamshere, M.L., Walters, J.T., Smith, R., Richards, A.L., Green, E., Grozeva, D., Jones, I., Forty, L., Jones, L., Gordon-Smith, K., Riley, B., O'Neill, F.A., Kendler, K.S., Sklar, P., Purcell, S., Kranz, J., Schizophrenia Psychiatric Genome-wide Association Study, C, Wellcome Trust Case Control, C, Wellcome Trust Case Control, C, Morris, D., Gill, M., Holmans, P., Craddock, N., Corvin, A., Owen, M.J., O'Donovan, M.C., 2013. Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the schizophrenia PGC. Mol. Psychiatry 18 (6), 708–712.

Harms, M.P., Wang, L., Campanella, C., Aldridge, K., Moffitt, A.J., Kuelper, J., Ratnanather, J.T., Miller, M.I., Barch, D.M., Csernansky, J.G., 2010. Structural abnormalities in gyri of the prefrontal cortex in individuals with schizophrenia and their unaffected siblings. Br. J. Psychiatry J. Ment. Sci. 196 (2), 150–157.
Hartberg, C.B., Lawyer, G., Nyman, H., Jonsson, E.G., Haukvik, U.K., Saetre, P., Bjerkan, P.S., Andreassen, O.A., Hall, H., Agartz, I., 2010. Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. Psychiatry Res. 182 (2), 123–133.
Heilbronner, U., Munte, T.F., 2013. Rapid event-related near-infrared spectroscopy detects age-related qualitative changes in the neural correlates of response inhibition. NeuroImage 65, 408–415.
Hell, J.W., Westenbroek, R.E., Warner, C., Ahlijanian, M.K., Prystay, W., Gilbert, M.M., Snutch, T.P., Catterall, W.A., 1993. Identification and differential subcellular localization of the neuronal class C and class D L-type calcium channel alpha 1 subunits. J. Cell Biol. 123 (4), 949–962.
Henik, A., Salo, R., 2004. Schizophrenia and the stroop effect. Behav. Cogn. Neurosci. Rev. 3 (1), 42–59.
Hepp, H.H., Maier, S., Hermle, L., Spitzer, M., 1996. The Stroop effect in schizophrenic patients. Schizophr. Res. 22 (3), 187–195.
Higo, T., Mars, R.B., Boorman, E.D., Buch, E.R., Rushworth, M.F., 2011. Distributed and causal influence of frontal operculum in task control. Proc. Natl. Acad. Sci. U. S. A. 108 (10), 4230–4235.
Hu, K., Lijffijt, M., Beauchaine, T.P., Fan, Z., Shi, H., He, S., 2015. Influence of empathetic pain processing on cognition in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 265 (7), 623–631.
Jang, K.E., Tak, S., Jung, J., Jang, J., Jeong, Y., Ye, J.C., 2009. Wavelet minimum description length detrending for near-infrared spectroscopy. J. Biomed. Opt. 14 (3), 034004.
Jonides, J., Nee, D.E., 2006. Brain mechanisms of proactive interference in working memory. Neuroscience 139 (1), 181–193.
Jonides, J., Smith, E.E., Marshuetz, C., Koeppe, R.A., Reuter-Lorenz, P.A., 1998. Inhibition in verbal working memory revealed by brain activation. Proc. Natl. Acad. Sci. U. S. A. 95 (14), 8410–8413.
Knochel, C., Reuter, J., Reinke, B., Stablein, M., Marbach, K., Feddern, R., Kuhlmann, K., Alves, G., Prvulovic, D., Wenzler, S., Linden, D.E., Oertel-Knochel, V., 2016. Cortical thinning in bipolar disorder and schizophrenia. Schizophr. Res. 172 (1–3), 78–85.
Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., Miyashita, Y., 1999. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain 122 (Pt 5), 981–991.
Krabbendam, L., O'Daly, O., Morley, L.A., van Os, J., Murray, R.M., Shergill, S.S., 2009. Using the Stroop task to investigate the neural correlates of symptom change in schizophrenia. Br. J. Psychiatry J. Ment. Sci. 194 (4), 373–374.
Krug, A., Nieratschker, V., Markov, V., Krach, S., Jansen, A., Zerres, K., Eggermann, T., Stocker, T., Shah, N.J., Treutlein, J., Muhleisen, T.W., Kircher, T., 2010. Effect of CACNA1C rs1006737 on neural correlates of verbal fluency in healthy individuals. NeuroImage 49 (2), 1831–1836.
Krug, A., Witt, S.H., Backes, H., Dietsche, B., Nieratschker, V., Shah, N.J., Nothen, M.M., Rietschel, M., Kircher, T., 2014. A genome-wide supported variant in CACNA1C influences hippocampal activation during episodic memory encoding and retrieval. Eur. Arch. Psychiatry Clin. Neurosci. 264 (2), 103–110.
Kubicki, M., McCarley, R.W., Nestor, P.G., Huh, T., Kikinis, R., Shenton, M.E., Wible, C.G., 2003. An fMRI study of semantic processing in men with schizophrenia. NeuroImage 20 (4), 1923–1933.
Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C., van der Kouwe, A.J., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 60 (9), 878–888.
Leung, H.C., Skudlarski, P., Gatenby, J.C., Peterson, B.S., Gore, J.C., 2000. An event-related functional MRI study of the stroop color word interference task. Cereb. Cortex 10 (6), 552–560.
Ma, H., Cohen, S., Li, B.X., Tsien, R.W., 2013. Exploring the dominant role of Cav1 channels in signalling to the nucleus. Biosci. Rep. 33, 97–101.
Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch. Gen. Psychiatry 66 (8), 811–822.
Moosmang, S., Haider, N., Klugbauer, N., Adelsberger, H., Langwieser, N., Muller, J., Stiess, M., Marais, E., Schulla, V., Lacinova, L., Goebbels, S., Nave, K.A., Storm, D.R., Hofmann, F., Kleppisch, T., 2005. Role of hippocampal Cav1.2 Ca2+ channels in NMDA receptor-independent synaptic plasticity and spatial memory. J. Neurosci. 25 (43), 9883–9892.
Muhle-Karbe, P.S., Derrfuss, J., Lynn, M.T., Neubert, F.X., Fox, P.T., Brass, M., Eickhoff, S.B., 2016. Co-activation-based parcellation of the lateral prefrontal cortex delineates the inferior frontal junction area. Cereb. Cortex 26 (5), 2225–2241.
Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese 3rd, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165 (2), 203–213.
Oertel-Knochel, V., Knochel, C., Rotarska-Jagiela, A., Reinke, B., Prvulovic, D., Haenschel, C., Hampel, H., Linden, D.E., 2013. Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum. Cereb. Cortex 23 (1), 61–70.
Okada, E., Delpy, D.T., 2003. Near-infrared light propagation in an adult head model. I. Modeling of low-level scattering in the cerebrospinal fluid layer. Appl. Opt. 42 (16), 2906–2914.
Park, J.H., Gail, M.H., Weinberg, C.R., Carroll, R.J., Chung, C.C., Wang, Z., Chanock, S.J., Fraumeni Jr., J.F., Chatterjee, N., 2011. Distribution of allele frequencies and effect sizes and their interrelationships for common genetic susceptibility variants. Proc. Natl. Acad. Sci. U. S. A. 108 (44), 18026–18031.
Paulus, F.M., Bedenbender, J., Krach, S., Pyka, M., Krug, A., Sommer, J., Mette, M., Nothen, M.M., Witt, S.H., Rietschel, M., Kircher, T., Jansen, A., 2014. Association of rs1006737 in CACNA1C with alterations in prefrontal activation and fronto-hippocampal connectivity. Hum. Brain Mapp. 35 (4), 1190–1200.
Perlstein, W.M., Carter, C.S., Barch, D.M., Baird, J.W., 1998. The Stroop task and attention deficits in schizophrenia: a critical evaluation of card and single-trial Stroop methodologies. Neuropsychology 12 (3), 414–425.
Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kahler, A.K., Akterin, S., Bergen, S.E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Multicenter Genetic Studies of Schizophrenia, C, Levinson, D.F., Gejman, P.V., Kendler, K.S., Laurent, C., Mowry, B.J., O'Donovan, M.C., Owen, M.J., Pulver, A.E., Riley, B.P., Schwab, S.G., Wildenauer, D.B., Dudbridge, F., Holmans, P., Shi, J., Albus, M., Alexander, M., Campion, D., Cohen, D., Dikeos, D., Duan, J., Eichhammer, P., Godard, S., Hansen, M., Lerer, F.B., Liang, K.Y., Maier, W., Mallet, J., Nertney, D.A., Nestadt, G., Norton, N., O'Neill, F.A., Papadimitriou, G.N., Ribble, R., Sanders, A.R., Silverman, J.M., Walsh, D., Williams, N.M., Wormley, B., Psychosis Endophenotypes International, C, Arranz, M.J., Bakker, S., Bender, S., Bramon, E., Collier, D., Crespo-Facorro, B., Hall, J., Iyegbe, C., Jablensky, A., Kahn, R.S., Kalaydjieva, L., Lawrie, S., Lewis, C.M., Lin, K., Linszen, D.H., Mata, I., McIntosh, A., Murray, R.M., Ophoff, R.A., Powell, J., Rujescu, D., Van Os, J., Walshe, M., Weisbrod, M., Wiersma, D., Wellcome Trust Case Control, C, Donnelly, P., Barroso, I., Blackwell, J.M., Bramon, E., Brown, M.A., Casas, J.P., Corvin, A.P., Deloukas, P., Duncanson, A., Jankowski, J., Markus, H.S., Mathew, C.G., Palmer, C.N., Plomin, R., Rautanen, A., Sawcer, S.J., Trembath, R.C., Viswanathan, A.C., Wood, N.W., Spencer, C.C., Band, G., Bellenguez, C., Freeman, C., Hellenthal, G., Giannoulatou, E., Pirinen, M., Pearson, R.D., Strange, A., Su, Z., Vukcevic, D., Donnelly, P., Langford, C., Hunt, S.E., Edkins, S., Gwilliam, R., Blackburn, H., Bumpstead, S.J., Dronov, S., Gillman, M., Gray, E., Hammond, N., Jayakumar, A., McCann, O.T., Liddle, J., Potter, S.C., Ravindrarajah, R., Ricketts, M., Tashakkori-Ghanbaria, A., Waller, M.J., Weston, P., Widaa, S., Whittaker, P., Barroso, I., Deloukas, P., Mathew, C.G., Blackwell, J.M., Brown, M.A., Corvin, A.P., McCarthy, M.I., Spencer, C.C., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E., Purcell, S., McCarroll, S.A., Sklar, P., Hultman, C.M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (10), 1150–1159.
Schizophrenia Psychiatric Genome-Wide Association Study, C, 2011. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43 (10), 969–976.
Schizophrenia Working Group of the Psychiatric Genomics, C, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427.
Sinnegger-Brauns, M.J., Huber, I.G., Koschak, A., Wild, C., Obermair, G.J., Einzinger, U., Hoda, J.C., Sartori, S.B., Striessnig, J., 2009. Expression and 1,4-dihydropyridine-binding properties of brain L-type calcium channel isoforms. Mol. Pharmacol. 75 (2), 407–414.
Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 44 (1), 83–98.
Striessnig, J., Pinggera, A., Kaur, G., Bock, G., Tuluc, P., 2014. L-type Ca2+ channels in heart and brain. WIREs Membr. Transport Signaling 3 (2), 15–38.
Sullivan, P.F., Kendler, K.S., Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch. Gen. Psychiatry 60 (12), 1187–1192.
Sundermann, B., Pfleiderer, B., 2012. Functional connectivity profile of the human inferior frontal junction: involvement in a cognitive control network. BMC Neurosci. 13, 119.
Swick, D., Ashley, V., Turken, A.U., 2008. Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci. 9, 102.
Tak, S., Jang, J., Lee, K., Ye, J.C., 2010. Quantification of CMRO(2) without hypercapnia using simultaneous near-infrared spectroscopy and fMRI measurements. Phys. Med. Biol. 55 (11), 3249–3269.
Tak, S., Yoon, S.J., Jang, J., Yoo, K., Jeong, Y., Ye, J.C., 2011. Quantitative analysis of hemodynamic and metabolic changes in subcortical vascular dementia using simultaneous near-infrared spectroscopy and fMRI measurements. NeuroImage 55 (1), 176–184.
Taylor, S.F., Kornblum, S., Lauber, E.J., Minoshima, S., Koeppe, R.A., 1997. Isolation of specific interference processing in the Stroop task: PET activation studies. NeuroImage 6 (2), 81–92.
Thimm, M., Kircher, T., Kellermann, T., Markov, V., Krach, S., Jansen, A., Zerres, K., Eggermann, T., Stocker, T., Shah, N.J., Nothen, M.M., Rietschel, M., Witt, S.H., Mathiak, K., Krug, A., 2011. Effects of a CACNA1C genotype on attention networks in healthy individuals. Psychol. Med. 41 (7), 1551–1561.
Thompson-Schill, S.L., Swick, D., Farah, M.J., D'Esposito, M., Kan, I.P., Knight, R.T., 1998. Verb generation in patients with focal frontal lesions: a neuropsychological test of neuroimaging findings. Proc. Natl. Acad. Sci. U. S. A. 95 (26), 15855–15860.
Toronov, V., Webb, A., Choi, J.H., Wolf, M., Michalos, A., Gratton, E., Hueber, D., 2001. Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. Med. Phys. 28 (4), 521–527.
Tsuchida, A., Fellows, L.K., 2013. Are core component processes of executive function dissociable within the frontal lobes? Evidence from humans with focal prefrontal damage. Cortex 49 (7), 1790–1800.
Ullsperger, M., von Cramon, D.Y., 2001. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. NeuroImage 14 (6), 1387–1401.
Wang, F., McIntosh, A.M., He, Y., Gelernter, J., Blumberg, H.P., 2011. The association of genetic variation in CACNA1C with structure and function of a frontotemporal system. Bipolar Disord. 13 (7–8), 696–700.

Westerhausen, R., Kompus, K., Hugdahl, K., 2011. Impaired cognitive inhibition in schizophrenia: a meta-analysis of the Stroop interference effect. Schizophr. Res. 133 (1–3), 172–181.

Wheeler, D.G., Groth, R.D., Ma, H., Barrett, C.F., Owen, S.F., Safa, P., Tsien, R.W., 2012. Ca(V)1 and Ca(V)2 channels engage distinct modes of Ca(2+) signaling to control CREB-dependent gene expression. Cell 149 (5), 1112–1124.

Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited–again. NeuroImage 2 (3), 173–181.

Ye, J.C., Tak, S., Jang, K.E., Jung, J., Jang, J., 2009. NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. NeuroImage 44 (2), 428–447.

Yoshimizu, T., Pan, J.Q., Mungenast, A.E., Madison, J.M., Su, S., Ketterman, J., Ongur, D., McPhie, D., Cohen, B., Perlis, R., Tsai, L.H., 2015. Functional implications of a psychiatric risk variant within CACNA1C in induced human neurons. Mol. Psychiatry 20 (2), 162–169.

Yu, P., Chen, X., Zhao, W., Zhang, Z., Zhang, Q., Han, B., Zhai, J., Chen, M., Du, B., Deng, X., Ji, F., Wang, C., Xiang, Y.T., Li, D., Wu, H., Li, J., Dong, Q., Chen, C., 2016. Effect of rs1063843 in the CAMKK2 gene on the dorsolateral prefrontal cortex. Hum. Brain Mapp. 37 (7), 2398–2406.

Zamponi, G.W., Striessnig, J., Koschak, A., Dolphin, A.C., 2015. The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. Pharmacol. Rev. 67 (4), 821–870.

Zhang, Z., Chen, X., Yu, P., Zhang, Q., Sun, X., Gu, H., Zhang, H., Zhai, J., Chen, M., Du, B., Deng, X., Ji, F., Wang, C., Xiang, Y., Li, D., Wu, H., Li, J., Dong, Q., Chen, C., 2015. Evidence for the contribution of NOS1 gene polymorphism (rs3782206) to prefrontal function in schizophrenia patients and healthy controls. Neuropsychopharmacology 40 (6), 1383–1394.

Zhang, Z., Chen, X., Yu, P., Zhang, Q., Sun, X., Gu, H., Zhang, H., Zhai, J., Chen, M., Du, B., Deng, X., Ji, F., Wang, C., Xiang, Y., Li, D., Wu, H., Li, J., Dong, Q., Chen, C., 2016. Effect of rs1344706 in the ZNF804A gene on the connectivity between the hippocampal formation and posterior cingulate cortex. Schizophr. Res. 170 (1), 48–54.

Zheng, F., Zhang, Y., Xie, W., Li, W., Jin, C., Mi, W., Wang, F., Ma, W., Ma, C., Yang, Y., Du, B., Li, K., Liu, C., Wang, L., Lu, T., Zhang, H., Wang, Y., Lu, L., Lv, L., Zhang, D., Yue, W., 2014. Further evidence for genetic association of CACNA1C and schizophrenia: new risk loci in a Han Chinese population and a meta-analysis. Schizophr. Res. 152 (1), 105–110.

Zheng, F., Cui, Y., Yan, H., Liu, B., Jiang, T., 2016. The effects of a genome-wide supported variant in the CACNA1C gene on cortical morphology in schizophrenia patients and healthy subjects. Sci. Rep. 6, 34298.