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ORIGINAL RESEARCH

Genetic Effects *of DISC1* and *G72 (DAOA)* on Visual Learning of Patients with Schizophrenia

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Background: Visual learning plays an important role in general populations and patients with schizophrenia. Genetic influences on visual learning remain unknown. Two functional single nucleotide polymorphisms (SNPs), Ser704Cys of the *DISC1* gene and M24 (rs1421292) of the *G72* gene, are strongly associated with pathogenesis and pathophysiology of schizophrenia. This study examined these two SNPs' effects on visual learning in schizophrenia patients.

Methods: Two hundred seventy-one patients (mean age, 37.0 years [SD = 9.3]; 159 men) with chronic schizophrenia were genotyped for the *DISC1* Ser704Cys and *G72* M24 SNPs and assessed for visual learning with Visual Reproduction II (delayed reproduction) of Wechsler Memory Scale – III (WMS-III). For comparison, verbal learning (using Word list II of WMS-III) and attention (by Continuous Performance Test) were also measured.

Results: The *DISC1* Ser carriers excelled *DISC1* Cys/Cys homozygotes in visual learning (p=0.004, effect size: 0.43), but not in other cognitive functions. *G72* M24 A-allele carriers and *G72* M24 T/T homozygotes performed similarly (effect size: 0.07). In SNP-SNP interaction analysis, the patients with Ser carrier_T/T had better visual learning than those with Cys/Cys_T/T (p=0.004, effect size: 0.70) and those with Cys/Cys_A-allele carrier (p=0.003, effect size: 0.65). Education had a positive effect (p=0.007), while negative symptoms had a negative effect (p<0.001) on visual learning.

Conclusion: The findings suggest that genetic variations in *DISC1* Ser704Cys and *G72* M24 affect visual learning in schizophrenia patients. The effect sizes of SNP-SNP interaction surpassed the sum (0.50) of effect sizes from two individual genes, suggesting synergistic *DISC1-G72* interaction.

Keywords: attention, *DISC1*, *G72*, visual and verbal learning, schizophrenia

Introduction

Visual learning plays an important role in daily life,[1] while schizophrenia is a debilitating disorder with significant visual learning dysfunction.[2] Visual learning, one of the seven cognitive domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition) of NIMH-recommended MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia),[3] has gained growing attention for search of endophenotypes of schizophrenia.[4–10] Three stages of visual learning/memory include encoding of visual perception, visual memory consolidation, and visual memory retrieval. Episodic visual memory encoding, involving visual attention and elaboration, relies heavily on the frontal lobes and visual association cortices.[11] Visual memory consolidation depends mainly on the

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right medial-temporal lobe (MTL), particularly the hippocampus.[11] The right MTL recapitulates the visual learning associated activation pattern and strengthens connections across the relevant lateral cortices.[11] MTLs and lateral cortices are necessary for retrieving unconsolidated and consolidated visual memories, respectively.[11] Visual memory impairments, mediated by organizational deficits,[5] reflect prefrontal cortex mediated executive dysfunction in patients with schizophrenia;[12] while deficits of visual perception are related with their premorbid social functioning,[13] illness severity and chronicity.[2] Whereas visual memory deficits reflect organization skill deficits,[5] memory encoding and consolidation act as prognostic predictors of the illness.[2,5] Of note, in patients with schizophrenia, visual memory declines with duration of illness.[5] In addition, both verbal and visual memory abnormalities are well-established features of the schizophrenia spectrum, such as schizotypal personality disorder.[6] Interestingly, visual memory and verbal memory show distinct generational trajectories and visual memory may offer a better potential than verbal memory to predict future risk of developing the disease.[9] Further, visual memory deficits are related with anhedonia in schizophrenia patients, but not with that in psychotic bipolar patients or healthy controls.[10] However, studies exploring visual learning/memory have been far less extensive and consistent than the studies on verbal memory.[14–16]

The *disrupted-in-schizophrenia* (*DISC1*) gene, disrupted by the chromosome 1 breakpoint of a balanced t (1;11) translocation,[17,18] and *G72* (also known as *D-amino acid oxidase activator, DAOA*) gene[15,19,20] have both been strongly associated with schizophrenia and hippocampal dysfunction. *DISC1* is expressed in neurons and glial cells, and greatly impacts the neurodevelopmental processes including neuritic outgrowth, neuronal migration, synaptogenesis, and glutamatergic transmission.[18] Glutamate synapse activation leads to N-methyl-D-aspartic acid receptor (NMDAR) triggered long-term potentiation. Reduced expression of *DISC1* binding patterns in postmortem frontal and parietal cortices and hippocampus of schizophrenia patients further implicates the role of *DISC1* in schizophrenia pathogenesis.[21] Altered *DISC1* expression in orbitofrontal cortex, linking to dorsolateral prefrontal cortex (DLPFC) and verbal working memory, has been reported in schizophrenia.[14] *DISC1* genetic variance was associated with neurocognitive dysfunctions, such as deficits in the P300 event-related potential, verbal working memory, verbal attention,[4] and verbal memory,[14] but not yet visual learning/memory in schizophrenia. One study reported the association between *DISC1* haplotype, HEP3 (containing two SNPs, T-A allele at rs751229 and rs3738401), and poor short-term visual attention and visual working memory.[4] A common *DISC1* nonsynonymous SNP at amino acid 704 (Ser704Cys, rs821616) leading to a serine-to-cystine substitution is associated with altered hippocampal structure and function, impaired verbal working memory, and increased risk for schizophrenia.[22] *DISC1*-Cys allele was also associated with reduced hippocampal grey matter volume[23] and impaired cognitive ability in women.[24] Since visual memory consolidation depends mainly on the right MTL, particularly the hippocampus,[11] the potential influence of the *DISC1* SNP at amino acid 704 on visual memory deserves study too.

Another susceptibility gene, *G72*, modulates NMDAR neurotransmission via activating D-amino acid oxidase (DAAO) to oxidize D-serine, a potent NMDAR agonist,[25] to hydroxy-pyruvate.[26] Hence, *G72* expression with DAAO activation results in decreased NMDAR neurotransmission and schizophrenia phenotype presentation.[25] However, G72 regulation for DAAO activity requires further elucidation.[26] Schizophrenia is strongly associated with markers in the 3′ region of *G72*, especially marker M24 (rs1421292).[19] *G72* genetic abnormalities lead to altered D-serine metabolism and NMDAR neurotransmission.[26] *G72* regulates prefrontal synaptic dopamine and is upregulated in postmortem DLPFC of schizophrenia patients.[21] T-allele of M24 compared to A-allele predicts cognitive impairments and altered cortical activity.[19] T/T genotype of *G72* M24 genetic variance has been associated with decreased hippocampal activation, increased frontal lobe activation during episodic memory encoding and retrieval,[19] verbal fluency tasks[16] and verbal sentence completion tasks[15] in both healthy and high-risk individuals. *G72* M24 genetic variances also affect hippocampal complex and prefrontal cortex function in high-risk individuals.[15] As aforementioned, since visual memory consolidation depends mainly on the hippocampus,[11] the potential influence of *G72* M24 genetic variance on visual memory deserves study too.

Structural and functional studies have converged on the potential regulatory effects of *DISC1* and *G72* on verbal learning/memory.[14,19] *DISC1* genetic variances, not including the Ser704Cys SNP, have been associated with visual attention,[4] while there is no study on *G72* and visual learning/memory. Hence, whether *DISC1* and *G72*

influence visual learning/memory in schizophrenia patients deserves further study. To our knowledge, this is the first genetic study on visual learning in humans, aiming to investigate the role of Ser704Cys SNP (rs821616) of *DISC1* and M24 SNP (rs1421292) of *G72* in neurocognition, with emphasis on visual learning/memory, of patients with schizophrenia.

Methods

Subjects

The study was approved by institutional review board of China Medical University Hospital, Taiwan and conducted in accordance with the current revision of the Declaration of Helsinki.

Han Chinese schizophrenia patients were recruited with the inclusion criteria of 1) having sufficient education to communicate effectively and complete the assessments of the study; 2) being interviewed by experienced research psychiatrist with the Structured Clinical Interview for DSM-IV[27] to confirm the diagnosis of schizophrenia and exclude other psychiatric disorders, including personality disorders and mental retardation; 3) aged 18–65; 4) physically healthy determined by physical examination and laboratory tests (normal blood routine and biochemical tests); and 5) keeping stable dosages of antipsychotic treatment for at least 2 months before enrollment. Patients were excluded when they currently 1) presented with other comorbid psychiatric disorders, substance use disorder or mental retardation; 2) had other existing physical or neurological illnesses; and 3) failed to cooperate with the study.

The participants were 271 unrelated patients with chronically stable schizophrenia, 159 men and 112 women, with a mean age of 37.0 years (SD = 9.3), a mean education level of 11.2 years (SD = 2.4), and a mean duration of illness of 162.0 months (SD = 102.2). After complete description, all participants provided written informed consent.

Clinical Assessments

The Positive and Negative Syndrome Scale (PANSS)[28] was used to assess the clinical symptoms. Clinical ratings were performed by trained and experienced research psychiatrists. Inter-rater reliability was analyzed with the ANOVA test. Only raters reaching intra-class correlation coefficients of ≥0.90 during pre-study training were allowed for rating. Raters met at least once a month for training and reliability re-testing to maintain high interrater reliability and prevent rater drift.

Measurement of Neurocognitive Function

Patients' cognitive functions, including verbal learning, visual learning, and attention were measured. Word listing II of Wechsler Memory Scale – III (WMS-III)[29] was applied to measure "verbal learning"; Visual Reproduction II of the WMS-III was used for "visual learning"; and the d' value of Continuous Performance Test (CPT)[30] was employed to assess "sustained attention."

In "Word list I" of WMS-III, the subjects recalled immediately after a word list of 12 items was read to them each time for four times, and the Word list I score was the number of items correctly recalled after four repeats of the 12 items. A second "interfering" word list without any of the previous 12 items was introduced to the subjects and subjects needed to recall the words from the first word list. In "Word list II," the subjects recalled as much of the first word list after a 30-min interval since the first list had been initially introduced, and the Word list II score was the number of items correctly recalled after the 30-min interval.

In "Visual Reproduction I," subjects drew a figure 10 s after the figure was shown to them. Subjects were shown a total of 7 figures. The first 3 figures were shown with a one figure per page display and the remaining 4 figures with a 2 figures per page display. In the "Visual Reproduction II or delayed visual reproduction," the subjects recalled and drew the figures 30 mins later.

Genotyping

For determining the genotype of *DISC1*-Ser704Cys SNP (rs821616) from venous blood samples, polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) analysis procedures[17] were applied with *DISC1*-F (AGGCCATGTGAAAAGGACAG) and *DISC1*-R (GTCTC AGCTGCAAGTGTCCA). PCR conditions were: 95ºC for 4 min initial heating, followed by 35 cycles of 95ºC for 30 sec, 61ºC for 30 sec, and 72ºC for 30 sec; and finally, 72ºC for 7 min. Subjects with Cys/Cys-*DISC1* allele gave rise bands of 294 base pairs (bp); Ser/Ser allele, 225 bp and 69 bp; and Ser/Cys allele, 294 bp, 225 bp and 69 bp.

The G72 M24 SNP genotyping was performed using the Taqman SNP genotyping assay (ABI: Applied Biosystems Inc., Foster City, CA, USA). The primers and probes of SNPs were from ABI Company. The PCR reaction was conducted in 15μL reaction volume, containing 0.4 μL

DNA sample (50 ng), 7.5 μL Master mix (Roche), and 0.4 μL 40x primer pairs and probes. A pre-incubation at 95°C for 10 min was employed to activate the Hot-Start DNA polymerase and denature DNA and was followed by 40 amplification cycles of 92°C denaturation for 15 sec, and 60°C for 60 sec. The probe fluorescence signal detection was performed using the ABI Prism 7500 Real-Time PCR System. The results were analyzed with SDS software 2.0 using the allelic discrimination assay program.

Data Analysis

All statistical analysis was carried out with Statistical Package for the Social Science (SPSS), version 22.0 for windows. Deviation of the genotype counts from the Hardy–Weinberg equilibrium was tested using a Chi-square goodness-of-fit test. Demographic and clinical characteristics and cognitive function of patients among genotypes were compared by Chi-square test, Fisher's exact test, independent sample *t* test or one-way ANOVA where appropriate. Here, since the number of subjects homozygous for Ser allele was small (n= 5), we grouped Ser carriers together; that is, *DISC1*-Ser/Ser and *DISC1*-Ser/Cys patients were combined as *DISC1*-Ser carriers to compare with *DISC1*-Cys/Cys homozygotes.[24] Meanwhile, A-allele carriers of *G72* M24 (A/A and A/T) were combined and compared to *G72* M24-T/T homozygotes.[16]

Multiple regressions were used to compare neurocognitive functions between *DISC1*-Ser carrier and *DISC1* Cys/Cy homozygotes, between *G72* M24-A carriers and *G72* M24-T/T homozygotes, and among four diplotype groups (1. *DISC*-Ser carrier with *G72*-M24 T/T, 2. *DISC1*-Ser carrier with *G72* M24-A carrier, 3. *DISC1*-Cys/Cys with *G72* M24-T/T, and 4. *DISC1*-Cys/Cys with *G72* M24-A carrier) while controlling confounding factors, such as age, onset age, typical/atypical antipsychotics, education years, PANSS-Positive subscale score and PANSS-Negative subscale score. Age,[31] onset age,[32] illness duration,[33] typical/atypical antipsychotic,[34] education years[35] and active symptoms[2] have been associated with effects on cognitive function and visual learning/memory.

Results

Genotype Distribution

The genotype distribution of the *DISC1*-Ser704Cys SNP was Cys/Cys in 212 patients and Ser carrier in 59 patients (including 54 Ser/Cys and 5 Ser/Ser 59 patients). The distribution was in accordance with Hardy–Weinberg equilibrium ($\chi^2 = 0.66$, d.f.= 1, $p > 0.05$). The frequency (98%) of Cys allele was similar to those of other Han Chinese studies,[17,36] but higher than that (69.2%) in Caucasian populations.[22]

Regarding the genotype distribution of *G72* M24 SNP, there were 161 A-allele carriers (48 AA and 113 TA) and 110 TT homozygotes. The A allele frequency (59%) was lower than that of the Japanese population (75%),[37] but higher than that (44%) in Caucasian populations.[38] This is the first study exploring *G72* M24 SNP on Han Chinese patients with schizophrenia.

Cognitive Functions Among Genotype Groups

As shown in Figure 1, the three *DISC1* genotypes showed an allele-dose effect on Visual Reproduction II performance, while the three *G72* M24 genotypes had no significant influence. Univariate regression was used for comparison among the three genotype groups: compared to the performance (4.7 ±2.6) of the patients who carried no Ser allele (Cys/Cys homozygotes), those who carried 1 Ser allele (Ser/Cys heterozygotes) had better visual learning ability (5.8±2.7, t=2.593, P=0.010) and those who carried 2 ser alleles (Ser/Ser homozygotes) also tended to perform better (6.8±3.9, t=1.735, P=0.084), albeit insignificantly perhaps due to the very small sample size of the Ser/Ser group (n=5). We, therefore, grouped Ser carriers (*DISC1* Ser/Ser and *DISC1* Ser/Cys patients) as a group to compare with *DISC1* Cys/Cys homozygotes;[24] meanwhile, A-allele carriers of *G72* M24 (A/A and A/T) were combined and compared to *G72* M24 T/T homozygotes (Table 1).[16]

Demographic characteristics, clinical manifestations, CPT, and Word list II between *DISC1* genotypes (Cys homozygotes vs Ser carriers) and between *G72* M24 genotypes (TT homozygotes vs A carriers) were similar (Table 1). Of note, the Ser carriers excelled Cys homozygotes in Visual Reproduction II performance (t= 2.912, p=0.004), while TT homozygotes and A carriers performed similarly (Table 1).

Cognitive Functions Among Diplotype Groups

Demographic characteristics, clinical manifestations, CPT, and Word list II among the 4 diplotype groups (Ser carrier_TT, Ser carrier_A carrier, Cys/Cys_TT, Cys/Cys_A carrier) were similar (Table 2). However, the four diplotype groups differed significantly in Visual Reproduction II performance (F= 3.621, p=0.014) (Table 2).

Moreover, Cys/Cys_T/T group (4.7±2.5, p=0.004) and Cys/Cys_A carrier group (4.8±2.7, p=0.003), yet not Ser

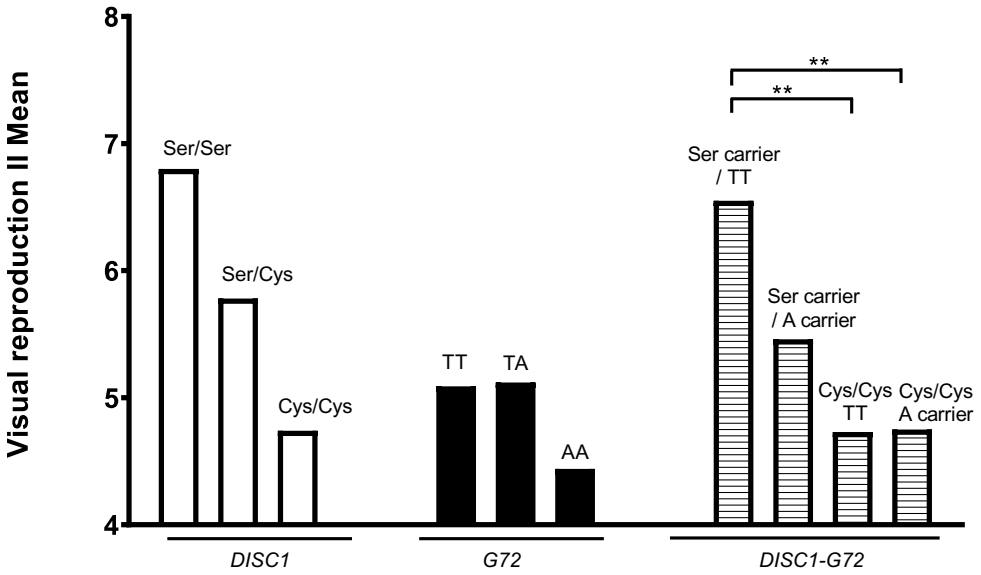

Figure 1 Influences of DISC1 Ser704Cy genotypes, G72 M24 (rs1421292) genotypes, and DISC1 Ser704Cys_G72 M24 interactions on visual learning, represented by means of Visual Reproduction II of Wechsler Memory Scale – III. **p< 0.01.

carrier_A carrier group (5.5±2.3, p=0.125), had poorer Visual Reproduction II scores when compared to Ser carrier_T/T group (6.6±3.1) by univariate regression (Figure 1). Furthermore, after controlling demographic and clinical variables (Table 3) using multiple regression, education duration had positive effect (p=0.007), while negative symptoms (p< 0.001), Cys/Cys_T/T (p=0.010) diplotype, and Cys/Cys_A carrier (p=0.002) diplotype had negative effects on Visual Reproduction II scores (Table 3).

Synergistic Effect of DISC1Ser704Cys and G72 M24 SNP on Visual Learning

We then evaluated genetic effects on delayed visual memory by the effect size of the two SNPs and their combination on delayed visual memory. The effect size on delayed

Table 1 Demographic Characteristics, Clinical Features, and Cognitive Functions of Schizophrenia Patients with *DISC1* Ser704Cys and *G72* M24 Genotypes

Variable	*Disc1*			*G72 M24*		
	Cys/Cys	**Ser Carrier**	**P-value**	**T/T**	**A Carrier**	**P-value**
N	212	59		110	161	
Sex (F/M), No.	82/130	30/29	0.093[a]	48/62	64/97	0.52[a]
Age, y, mean (SD)	36.8 (9.3)	37.8 (9.4)	0.47[b]	37.6 (9.7)	36.6 (9.0)	0.47[b]
Education, y	11.2 (2.4)	11.1 (2.5)	0.73[b]	10.9 (2.3)	11.4 (2.4)	0.056[b]
Age at illness onset, y	23.3 (6.3)	23.3 (6.4)	1.00[b]	23.0 (6.1)	23.5 (6.4)	0.51[b]
Illness duration, m	161.3(101.9)	164.5(104.1)	0.83[b]	167.1 (108.1)	158.5 (98.1)	0.51[b]
Atypical/Typical Antipsychotics/ Drug naive	150/57/5	44/13/2	0.68[c]	80/27/3	114/43/4	0.93[c]
PANSS-Positive	20.2 (4.6)	19.9 (4.7)	0.65[b]	20.7 (4.9)	19.7 (4.4)	0.094[b]
Negative	23.7 (5.5)	24.0 (4.7)	0;68[b]	23.7 (5.0)	23.7 (5.5)	0.99[b]
CPT	1.54 (1.6)	1.3 (1.5)	0.41[b]	1.4 (1.6)	1.6 (1.6)	0.28[b]
Word list II	4.8 (3.2)	4.9 (2.8)	0.68[b]	4.7 (3.5)	4.8 (2.8)	0.80[b]
Visual II	4.7 (2.6)	5.9 (2.7)	**0.004**[b,**]	5.1 (2.7)	4.9 (2.6)	0.59[b]

Notes: Bold values indicate statistical significance, **P<0.01. [a]Chi-square test, [b]Independent sample *T* test (*T*-Test), [c]Fisher's exact test

Abbreviations: PANSS-Positive, Positive and Negative Syndrome Scale-Positive subscale; PANSS-Negative, Positive and Negative Syndrome Scale-Negative subscale; CPT, Continuous Performance Test (d' value); Word list II, Word list II of Wechsler Memory Scale – III (WMS-III) (standardized score); Visual II, Visual Reproduction II of WMS-III (standardized score).

Table 2 Demographic Characteristics, Clinical Features, and Cognitive Functions of Schizophrenia Patients with Different *DISC1* Ser704Cys and *G72* M24 Diplotypes

***DISC1, G72* M24 Diplotype**					
Variable	**Ser Carrier, TT**	**Ser Carrier, A Carrier**	**Cys/Cys, TT**	**Cys/Cys, A Carrier**	**p-value**
N	22	37	88	124	
Sex (F/M), No.	14/8	16/21	34/54	48/76	0.16[a]
Age, y, mean (SD)	38.2(10.4)	37.5 (8.9)	37.4 (9.6)	36.4 (9.1)	0.75[b]
Education, y	11.2 (2.7)	11.0 (2.4)	10.8 (2.2)	11.5 (2.5)	0.12[b*]
Age at illness onset, y	23.8 (7.6)	22.9 (5.7)	22.7 (5.7)	23.6 (6.6)	0.72[b]
Illness duration, m	152.6 (121.3)	171.6 (93.5)	170.7 (105.0)	154.5 (99.5)	0.62[b]
Atypical/Typical Antipsychotics/ Drug naive	19/3/0	25/10/2	61/24/3	89/33/2	0.60[c]
PANSS-Positive	19.7 (4.7)	20.0 (4.7)	20.9 (4.9)	19.7 (4.4)	0.25[b]
Negative	23.6 (5.2)	24.2 (4.5)	23.8 (4.9)	23.6 (5.8)	0.93[b]
CPT	1.0 (1.3)	1.6 (1.7)	1.5 (1.6)	1.6 (1.6)	0.38[b]
Word list II	5.0 (3.0)	4.9 (2.8)	4.7 (3.6)	4.8 (2.8)	0.97[b]
Visual II	6.6 (3.1)	5.5 (2.3)	4.7 (2.5)	4.8 (2.7)	**0.014**[b,*]

Notes: Bold values indicate statistical significance, *P<0.05. [a]Chi-square test, [b]Analysis of variance (ANOVA), [c]Fisher's exact test.
Abbreviations: PANSS-Positive, Positive and Negative Syndrome Scale-Positive subscale; PANSS-Negative, Positive and Negative Syndrome Scale-Negative subscale; CPT, Continuous Performance Test (d' value); Word list II, Word list II of Wechsler Memory Scale – III (WMS-III) (standardized score); Visual II, Visual Reproduction II of WMS-III (standardized score).

visual memory for *DISC1* Ser704Cys SNP was 0.43 and for *G72* M24 SNP was 0.07 (Figure 2). The additive effect size of both SNPs was 0.50 (= 0.43 + 0.07). Effect sizes of Cys/Cys_T/T (0.70) and Cys/Cys_A-allele (0.65) on delayed visual memory were greater than the additive effect size (0.50) (Figure 2). This implicated that the effect of *DISC1*Ser704Cys and *G72* on visual learning appeared to be synergistic.

Discussion

The first major finding of this study is that *DISC1*-Ser carriers performed better than *DISC1*-Cys/Cys homozygotes in visual learning (as represented by delayed visual reproduction), but not in verbal learning or attention. Secondly, the patients with the diplotype of *DISC1*-Ser carrier_*G72* M24-T/T surpassed *DISC1*-Cys/Cys_*G72* M24-T/T or *DISC1*-Cys/Cys_*G72* M24-A carrier in visual learning, with a larger effect size

Table 3 Clinical and Genetic Variables Affecting Visual Learning, Represented by Standardized Score of Delayed Visual Reproduction of Wechsler Memory Scale – III

Variable	**Beta (SE)**	**T**	**p-value**
Age	0.012 (0.049)	0.253	0.80
Education	0.183 (0.068)	2.712	**0.007****
Onset of age	0.043 (0.055)	0.784	0.43
Illness duration	−0.001 (0.004)	−0.076	0.94
Antipsychotics, typical/atypical/naive	0.207 (0.355)	0.584	0.56
PANSS-Positive	−0.029 (0.034)	−0.840	0.40
PANSS-Negative	−0.127 (0.030)	−4.228	**< 0.001*****
Ser Carrier, TT in *DISC1, G72* M24 diplotype	-		
Ser Carrier, A-Carrier	−0.815 (0.671)	−1.216	0.23
Cys/Cys, TT	−1.544 (0.595)	−2.593	**0.010***
Cys/Cys, A-Carrier	−1.774 (0.578)	−3.068	**0.002****

Notes: Bold values indicate statistical significance, *P<0.05, **P<0.01, ***P<0.001. Multiple regression was utilized to compare visual learning among schizophrenia patients with different *DISC1* Ser704Cys_*G72* M24 diplotypes. Education duration had a positive effect on visual learning (p= 0.007), while negative symptoms (p <0.001), Cys/Cys_T/T diplotype (p=0.010), and Cys/Cys_A-carrier diplotype (p=0.002) showed negative associations with visual learning.
Abbreviations: Typical, typical antipsychotics; atypical, atypical antipsychotics; naïve, antipsychotics naïve; PANSS-Positive, Positive and Negative Syndrome Scale-Positive subscale; PANSS-Negative, Positive and Negative Syndrome Scale-Negative subscale.

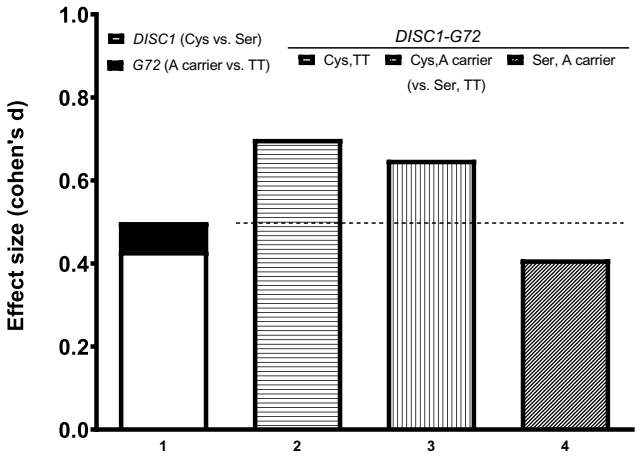

Figure 2 Effect sizes of the DISC1 genotype, G72 genotype, and DISC1_G72 interactions on visual learning, represented by Visual Reproduction II Wechsler Memory Scale – III. The dotted lines represent the sum of the effect sizes of the DISC1 and G72 individually. The DISC1 Ser carriers excelled DISC1 Cys/Cys homozygotes in visual learning (p=0.004, effect size: 0.43). Meanwhile, G72 M24 A-allele carriers and G72 M24 T/T homozygotes performed similarly (effect size: 0.07). In interaction analyses, the patients with Ser carrier_T/T had better visual learning than those with Cys/Cys_T/T (p= 0.004, effect size: 0.70) and those with Cys/Cys _A-allele carrier (p= 0.003, effect size: 0.65). Therefore, the effect sizes (0.70 and 0.65) of the DISC1_G72 interactions were larger than the sum (0.50 = 0.43 + 0.07) of the effect sizes of DISC1 and G72 individually, suggesting that the interactive gene effect of DISC1-G72 was more than addition.

than the sum of the effect sizes of *DISC1* and *G72* M24 individually, implying that the interactive gene effect of *DISC1-G72* was additive (Figure 2). The finding, therefore, lends support to the notion that both *DISC1* and *G72* are involved in visual learning and suggest that the two genes interact synergistically.

Visual memory/learning has not yet been widely investigated in schizophrenia patients. Hennah et al are the first to report the significance of visual attention and visual working memory in the pathogenesis of schizophrenia,[4] while others emphasized on verbal memory/learning.[14,15,19] Visual learning involves the ability to store and retrieve previously experienced visual sensations and perceptions when the stimuli that originally evoked them are no longer present.[11] And one, with intact memory encoding and consolidation, should be able to place in and retrieve memory information that resembles objects, places, animals or people in sort of a mental image from "the mind's eye."[11] Moreover, visual perception and memory often perceive image as a whole and not in pieces, and group images according to six features: proximity, similarity, closure, symmetry, common fate and continuity.[39] It is sensitive in ensembling characteristics of complex objects such as face,[39] and its impairments are associated with poor social functioning[13] and illness severity[2] in schizophrenia.

Furthermore, visual learning deficits, mediated by organization skill deficits[5] and poor memory encoding,[5] contribute to poor planning skills[5] and executive dysfunction.[12] Patients with schizophrenia often use a piecemeal approach and have difficultly processing the gestalt of a complex visual stimulus in visual learning evaluation.[7] Hence, impaired processing of global features in a local-global paradigm in these patients[40] often results in overemphasis on non-critical features and depletion of available attention resources before they can process the critical features or interpret wholes as meaningful gestalts;[40] which further implies their inefficient organizational strategy.[7] Deficits in visual perception, visual memory encoding and consolidation all contribute to visual learning deficits. Li et al also found that Cys-allele carriers have less efficient information transfer than Ser homozygotes.[41] Cys-allele carriers had a significantly lower global efficiency of their brain networks and decreased white matter integrity.[41]

Animal genetic study has demonstrated a close association of *DISC1*, cognitive functions, and hippocampal function/structure.[18] Human studies have also shown an association of several *DISC1* haplotypes, such as HEP1 (rs6675821, rs1000731, rs3890280), HEP2/HEP3 segment (rs1615409, rs766288, rs751229, rs3738401), with altered cognitive function.[4,14,24] Cys allele has been associated with impaired verbal learning/long-term memory in schizophrenia and normal controls;[14,24] while a few *DISC1* haplotypes, but not including the SNP of the current study, for example, HEP2/HEP3 segment (rs1615409, rs766288, rs751229, rs3738401), HEP3 (rs751229, rs3738401) and hCV1650649 were associated with visual attention/search, visual working memory, and visuospatial memory.[4,14] On the other hand, *G72* M24-TT homozygotes were associated with decreased hippocampal activation and increased prefrontal activation in fMRI during episodic memory encoding and retrieval, working memory and verbal completion tasks.[15,19,20] We are the first group to report the association of genetic effects between *DISC1* Ser704Cys SNP and *G72* M24 SNP and delayed visual memory/learning impairment. Interaction of the SNPs on visual memory was supported by a greater effect size of SNP combination (0.70, 0.65) than the sum of each SNP (0.50) (Figure 2). Unlike previous studies,[22,24] no association was shown between *DISC1* Ser704Cys SNP and *G72* M24 SNP, and verbal learning/memory. This may be due to different neuropsychological assessment tools used between ours and other studies.[4,14] In addition, verbal memory rather than visual memory might be more susceptible to antipsychotic (dopamine) effects.[42]

Finding of poorer visual learning and delayed visual memory in Cys allele carriers are consistent with previous

frontal-parietal network (insular cortex) disruption studies in schizophrenia patients,[43] where the insular cortex of the temporal cortex is implied for general consolidation of visual recognition memories.[43] Association of *DISC1* Ser704Cys SNP and *G72* M24 SNP and visual memory/learning impairment is further supported by the impact of the *DISC1* Ser704Cys SNP on visual memory associated brain structural changes[44] and the impact of the *G72* M24 SNP on memory task associated brain activations.[19] Cys allele has been associated with reduced supramarginal gyrus volume, which is part of inferior parietal lobe responsible for enactment effect specific for visual memory encoding.[45]

Visual memory recall predominantly activates the left superior frontal gyrus and the intraparietal cortex, whereas recall of visually learned locations activates the bilateral superior parietal cortices.[11] *DISC1* and *G72* genetic variances are closely associated with these visual memory-associated brain areas including insular cortex, medial superior frontal and prefrontal gyri, and hippocampus.[14,19,23] Ser/Ser homozygote with schizophrenia had similar or larger medial superior frontal gyrus and insular cortex volumes when compared with Cys carriers.[44] Moreover, *DISC1* Ser allele homozygotes compared to Cys allele carriers had greater hippocampal gray matter volume,[23] which further supported the possible concept that schizophrenia patients with Cys allele had poorer visual memory (Figure 1).

The study also found that longer education duration benefited visual learning (Table 3). This finding is consistent with previous studies implying that higher Intelligent Quotient (IQ) favors better delayed visual memory performance.[35] This study also found that negative symptoms had detrimental effects on visual learning. Negative symptoms have been associated with visual memory impairment in patients with schizophrenia.[2]

Limitations

This study has several limitations. Firstly, the distribution of Cys and Ser allele is different from the previous study.[22] Frequency of Cys homozygotes is higher, while Ser homozygotes is lower in our study. This may be explained by the Han Chinese ethnicity of the subjects. However, the distribution of the *DISC1* genotype is similar to the report of NCBI.[36] Moreover, there is no control group for this study. The reported effects of the studied SNPs on visual memory may be general effects for any subject, which would mean that they are not specific to schizophrenia. Inclusion of a control group in future replication study is needed. Thirdly, we used Word List of WMS-III rather than California Verbal Test to assess verbal memory due to the limited availability of the Chinese version of the California Verbal Test. However, the measures from the two tests were highly correlated.[46] Fourthly, the use of a single neuropsychological test to assess visual learning may be considered a shortcoming of the paper.

Conclusions

The present study is the first genetic study of visual memory in humans. It is also the first to investigate *G72* M24 SNP in Han Chinese patients with schizophrenia and the first to explore the relationship between *DISC1* Ser 704Cys and *G72* M24 genetic effects and visual memory in schizophrenia patients. Study findings indicated that schizophrenia patients with the Cys/Cys_T/T or Cys/Cys_A carrier had poorer visual learning. The combination of the two SNPs also supported an additive effect of the individual SNPs, suggesting that *DISC1* and *G72* might interact synergistically and thereby accounting for variance in hippocampal structure, function, and activation.[19,23] Callicot also suggested that the risk of developing schizophrenia and associated cognitive deficits may be due to haplotypes monitored by Ser704Cys rather than the SNP itself.[22] Thus, investigating the roles of other genetic variants of *DISC*[4,17,22] and their interactions with *G72* genetic variances[15,19,20] may further help search for the endophenotype and subtyping of schizophrenia patients and development of targeted treatments.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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