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Ocular and neural genes jointly regulate the visuospatial working memory in ADHD children

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Abstract

Objective Working memory (WM) deficits have frequently been linked to attention deficit hyperactivity disorder (ADHD). Despite previous studies suggested its high heritability, its genetic basis, especially in ADHD, remains unclear. The current study aimed to comprehensively explore the genetic basis of visual-spatial working memory (VSWM) in ADHD using wide-ranging genetic analyses.

Methods The current study recruited a cohort consisted of 802 ADHD individuals, all met DSM-IV ADHD diagnostic criteria. VSWM was assessed by Rey-Osterrieth complex figure test (RCFT), which is a widely used psychological test include four memory indexes: detail delayed (DD), structure delayed (SD), structure immediate (SI), detail immediate (DI). Genetic analyses were conducted at the single nucleotide polymorphism (SNP), gene, pathway, polygenic and protein network levels. Polygenic Risk Scores (PRS) were based on summary statistics of various psychiatric disorders, including ADHD, autism spectrum disorder (ASD), major depressive disorder (MDD), schizophrenia (SCZ), obsessive compulsive disorders (OCD), and substance use disorder (SUD).

Results Analyses at the single-marker level did not yield significant results ($5E-08$). However, the potential signals with P values less than $E-05$ and their mapped genes suggested the regulation of VSWM involved both ocular and neural system related genes, moreover, ADHD-related genes were also involved. The gene-based analysis found *RAB11FIP1*, whose encoded protein modulates several neurodevelopment processes and visual system, as significantly associated with DD scores ($P = 1.96E-06$, $P_{adj} = 0.036$). Candidate pathway enrichment analyses ($N = 53$) found that forebrain neuron fate commitment significantly enriched in DD ($P = 4.78E-04$, $P_{adj} = 0.025$), and dopamine transport enriched in SD ($P = 5.90E-04$, $P_{adj} = 0.031$). We also observed a significant negative relationship between DD scores and ADHD PRS scores ($P = 0.0025$, Empirical $P = 0.048$).

Conclusions Our results emphasized the joint contribution of ocular and neural genes in regulating VSWM. The study reveals a shared genetic basis between ADHD and VSWM, with GWAS indicating the involvement of ADHD-related genes in VSWM. Additionally, the PRS analysis identifies a significant relationship between ADHD-PRS and DD scores. Overall, our findings shed light on the genetic basis of VSWM deficits in ADHD, and may have important implications for future research and clinical practice.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly heritable disorder in children, with an approximately 7.2% prevalence [1]. Except for the main clinical features (i.e., age-inappropriate attention deficit, hyperactivity, and impulsivity), ADHD cases often display multiple neuropsychological deficits, including working memory (WM), planning, vigilance and inhibition [2].

Working memory is the capacity to manipulate some information and maintain other information simultaneously, including auditory-verbal working memory and nonverbal working memory [3]. Visual-spatial working memory (VSWM) is a kind of nonverbal working memory, refers to the ability of temporarily holding and manipulating visual and spatial information in the mind for use in ongoing tasks. Meta-analyses indicated that VSWM was impaired in ADHD individuals [4–7], and previous evidence showed a positive relationship between the severity of ADHD symptoms and VSWM deficits [8–10], suggesting VSWM might serve as one promising endophenotype for ADHD [4].

The Rey-Osterrieth Complex Figure (RCFT) is a validated and widely used measure of VSWM, developed by Rey [11]. The RCFT is capable of distinguishing between various aspects of VSWM, including the ability to retain the visual details of the figure, the ability to organize and integrate the different parts of the figure, and the ability to manipulate the figure mentally [12, 13]. Previous studies have consistently shown that ADHD individuals exhibit compromised performance on the RCFT task compared to typically developing (TD) individuals [14–16]. Specifically, deficits have been observed in the delayed scores and the organizational scores, indicating impairments in short-term working memory, global visual processing, and working memory integration [10, 14].

Visual-spatial working memory (VSWM) has been shown to be moderately to highly heritable by twin studies [17, 18]. At the molecular level, although the specific gene basis is still unknown, evidence from candidate gene-based analyses suggested that the dopaminergic circuit-related genes, which served as a main etiological pathway in ADHD, were involved [19]. Previous studies suggested the dopamine transporter (DAT) is a promising candidate risk gene in the etiological process of ADHD and has also been found to affect WM [20–23]. Dopamine receptor D1 (*DRD1*) gene, in which SNPs rs4532 and rs265978 moderated working memory improvements over development, also

predicted ADHD symptoms reduction [24]. The Associations between superior VSWM function and carrying Met in the Valine158Methionine (Val158Met) SNP (i.e., the rs4680) were also demonstrated [25–27].

However, recent evidence suggests that causal variants involved in complex traits are not restricted to specific core pathways [28]. Consistent with this notion, recent GWAS studies in VSWM also revealed a more complicated landscape, with not only dopaminergic genes, but also genes associated with synaptic plasticity, apolipoprotein, neurodegenerative disorders, and others being involved [29–32]. A GWAS study by Blokland et al. failed to test significant SNP associated with WM-related brain regions, however, nominal signals were found within genes *BANK1* and *FOXQ1*, which were involved in dopaminergic circuit and DNA binding, respectively [31]. Other two GWAS study found genes potentially associated with WM or visual-spatial ability at the 10^{-6} significant level, with implications in several psychiatric disorders and adrenergic receptor signaling pathway [29, 30]. A study published in 2022 found significant SNPs associated with verbal short-term memory, involving gene *APOE* and *CDH18*, which were responsible for Alzheimer's disorders and synaptic plasticity, respectively [32].

The manipulation of VSWM involves coordinated interactions of a distributed neural network, with the frontal lobe playing a central role as a control structure [33–36]. Dopamine transmission in the frontal cortex is critically for VSWM [37, 38], and the frontal lobe might serve as an important mediate factor between gene and WM deficits in ADHD [39]. An inverted U-shaped curve has been demonstrated in the relationship of frontal lobe functioning and WM performance, whereby both deficient and excessive amounts of prefrontal dopamine activity predict poor task performance [40].

The prefrontal lobe and dopaminergic circuit also involved in WM treatment response. Prior evidence has shown that improvements of VSWM after behavioral training was associated with changes in the density of cortical dopamine D1 receptors in prefrontal lobe [41]. Methylphenidate, a most widely used pharmaceutical treatment for ADHD, acts to increase the synaptic concentration of dopamine and noradrenaline could improve WM by altering regional cerebral flow (rCBF) in frontal and parietal lobes [42].

In conclusion, VSWM deficits in ADHD have a complex genetic basis that has not been fully understood.

Previous candidate-gene based studies have identified that ADHD related genes involved in the dopaminergic circuit in frontal lobe are associated with VSWM deficits in TD and ADHD. As a primary neuropsychological function and endophenotype, VSWM is considered to be less genetically complex than clinical phenotypes. Thus, deconstructing the genetic basis underlying VSWM might shed light on illuminating the pathophysiological processes of ADHD, helps establish objective neurocognitive diagnostic modalities and holds promises for the development of precise behavioral therapies.

The current study had two main objectives: (1) to identify genes associated with VSWM in individuals with ADHD using a genome-wide approach and explore the relevant biological processes, especially in dopaminergic circuit and forebrain development; (2) to disentangle overlapping and distinct genetic structures underlying different visuospatial processes involved in different parts of the RCFT task.

Materials and method

Participants

The cohort, which consisted of 802 ADHD cases (684 males, 85.3%) aged between 6 and 16 (9.9 ± 2.4) was recruited from the Child and Adolescent mental health center at Peking University Sixth Hospital. All patients met the diagnostic criteria of the Statistical Manual of Mental Disorders-IV (DSM-IV) for ADHD. The diagnosis was first made by a child psychiatrist and then confirmed by semi-structural interview using the Chinese version of KSADS-PL [43]. Patients with epilepsy, schizophrenia, pervasive development disorder or mental retardation ($IQ < 70$) were excluded [44]. Chinese Children version of the Wechsler Intelligence Scale (C-WISC, third edition) was used to assess IQ [45, 46]. The protocol was reviewed and approved by the Ethics Committee of Peking University Health Science Center. Written informed consent was obtained from the parents and from both the participants themselves and their parents if they were over 8 years old.

Neuropsychological test: rey-osterrieth complex figure test (RCFT)

All subjects finished the RCFT to evaluate VSWM. Subjects were instructed to remember the RCFT figure within 30 s and subsequently draw what they remembered immediately (without intervening distraction) and then a 20–30 min' delay (other tests were conducted during this delay) [10]. This test allowed us to observe subjects' immediate and delayed visual-spatial working memory performances [14]. Detail and structure scores were rated using 36-point and 6-point, respectively. The

36-point scoring system was initially devised by Osterrieth [50] and adapted by Booth [75], which could reflect both local and global VSWM. In the 36-point system, each figure is scored using 18 features: two points are given if the feature is placed correctly, and one point given if it is incomplete or placed poorly. The 6-point scoring system was devised by Binder [51], evaluated the accuracy and completeness for constructing five configurational elements and the addition of the base rectangle, which was used to evaluate the organizational strategies during RCFT task and global processing.

Genotyping quality control

The Omega DNA extraction Kit (Omega Bio-tek Inc., Doraville, GA) was used to extract genomic DNA from peripheral blood. The genomic DNA was genotyped using the Affymetrix 6.0 array with standard protocol at Capital Bio Ltd (Beijing) [44]. For quality control at the individual level, we excluded those with per-individual autosomal heterozygosity > 5 SD away from the mean, missing age or IQ information, as well as with a per-individual call rate $< 95\%$. For quality control at the SNP level, we included SNPs with call rate $> 98\%$, Hardy-Weinberg equilibrium test $P > 0.001$ [47], and minor allele frequency (MAF) $> 5\%$. After quality control, 802 ADHD patients remained. We then used MACH-admix 1.0 [48] to impute non-genotyped SNPs, using the ASN data from the Integrated Phase 1 Release of the 1000 Genome Projects (GRCh37/hg19) as the reference panel. Imputed SNPs with a squared correlation between imputed and true genotypes $r^2 < 0.6$ or SNPs with minor allele frequency < 0.05 were removed.

Principle component analysis (PCA) was performed to check population stratification. It was conducted using the SNPs with low linkage disequilibrium (LD, $MAF > 0.05$ and $r^2 < 0.05$ for each pair of SNPs) that were outside the 5 long-range LD regions using the EIGENSOFT 4.2 software [49], and validated by the Tracy-Widom test. There was no significant population stratification. Only the top 1 eigenvector was used as a covariate in subsequent statistical analyses.

Genome wide association analyses (GWAS) and annotation

The association between SNPs and the RCFT scores was conducted using the additive linear regression model by PLINK version 1.9 with age, sex and eigenvector one from principle component analysis as covariates [50–52]. In order to thoroughly address potential confounding effects of age, we conducted additional tests to examine the potential interaction relationships between age and genotypes (GWAS P-value less than $1E-05$).

We used three methods for gene mapping: positional mapping, eQTL mapping, and chromatin interaction

mapping. For positional mapping, we used a maximum distance of 10 kb [53]. The eQTL data and additional annotation data based on Hi-C results were obtained from 3D SNP and GTEx database ([54], <https://gtexportal.org/home/>). The Genecards website was used to check the function of genes [55, 56].

Gene-based analysis

We used Multi-marker Analysis of GenoMic Annotation (MAGMA) [57] for gene-based analysis. As recommended by de Leeuw et al. [57], we utilized the genotypic data as inputs instead of using GWAS summary statistics. The analytic procedure is as follows: SNPs were mapped to corresponding genes based on the NCBI 37.3 gene definitions, extending gene footprints by an additional 35 kilobase (kb) up- and 10 kb downstream as default. After SNP annotation, there were 18,177 genes that were covered by at least one SNP. Bonferroni correction was used, setting the two-side genome-wide threshold for significance at $2.75E-06$.

Candidate pathway-based analysis

Since previous evidence emphasized the critical role of dopaminergic circuits and the frontal lobe in the regulation of VSWM; and the current GWAS results indicated participation of ocular system (described in the result section). The current study included 53 Gene ontology biological process (GOBP) pathways involved in frontal lobe/forebrain (n=14), dopaminergic circuit (n=15), and eye/visual perception (n=24) as candidate pathways. Using MAGMA, we tested the association of candidate pathways with four RCFT scores. We adopted a Bonferroni correction, setting the threshold of significance $P < 9.43E-04$.

Protein–protein interaction (PPI) network construction

GeneMANIA (<http://www.genemania.org>) was adopted to construct the network of RCFT interactive proteins based on physical interactions, co-expression, predicted, co-localization, pathway, genetic interactions, and shared protein domains [58]. Visualization was implemented using Cytoscape [59].

Polygenic risk score (PRS)

Using the current cohort as target, we calculated PRSs using latest Psychiatric Genomic Consortium (PGC) GWAS statistics of six psychiatric disorders as base data,

including ADHD, autism spectrum disorder (ASD), obsessive compulsive disorder (OCD), major depression disorder (MDD), schizophrenia (SCZ), bipolar disorder (BIP), and substance use disorder (SUD) [60–66]. PRSice-2 [67] were used to calculate PRS scores and perform the high-resolution scoring method to select the most precise threshold for SNPs associated with each RCFT score (with lower and upper threshold as 0 and 0.5 respectively and the interval as 0.0001). The significance of the regression results was corrected by a permutation test with 10,000 replicates, an empirical P value less than 0.05 will be taken as significant. Pearson correlation rho was calculated between each index and psychiatric PRS scores and shown in a heatmap to aid in visualization.

Results

A total of 802 ADHD cases were included in the study, comprising 684 boys (85.3%) with an average age of 9.9 ± 2.4 years, and an average IQ was 104.5 ± 15.7 . The average points for DD (9.1 ± 0.2), DI (9.5 ± 0.2), SD (2.7 ± 0.1), and SI (2.9 ± 0.1) were also measured (Table 1).

Furthermore, we found significant positive relationships between ages and all four RCFT scores ($P_{\text{bon}} < 0.05$), suggesting that VSWM functions undergo dynamic changes over time (Fig. 1).

SNP, gene level associations and protein networks

Genome-wide association analyses, after quality control, were conducted for four RCFT scores. The SNP level association results did not reach genome-wide significance ($P < 5e-8$). However, we identified 26 potential risk loci with $P < 1e-05$ of DD, DI, SD, and SI (Table 2). None of the 26 risk loci showed potential interaction relationships between age and genotypes (interaction P values in all variants were larger than $10E-03$).

We identified 3, 6, 5, and 12 SNPs potentially associated with DD, DI, SD, and SI, respectively. Candidate risk genes for each locus were mapped and prioritized accordingly (Table 2). Interestingly, locus rs56111147 was potentially associated with three indexes except for SD, and it was located in the gene *TCL1B*, which has been previously linked to myopia [68]. Inspection of the mapped genes revealed that relevant genes were mainly related to the ocular and neural system (Fig. 2A). Additionally, delayed scores were associated mostly with neural system related genes, while most of the oculus related genes were relevant to immediate scores.

Table 1 Demographic characteristic and VSWM profile of the current cohort

Num of participants	Age (years)	Sex (boy: girl)	IQ	REYDD	REYDI	REYSD	REYSI
802	9.9 (2.4)	684:118	104.5 (15.7)	9.1 (0.2)	9.5 (0.2)	2.7 (0.1)	2.9 (0.1)

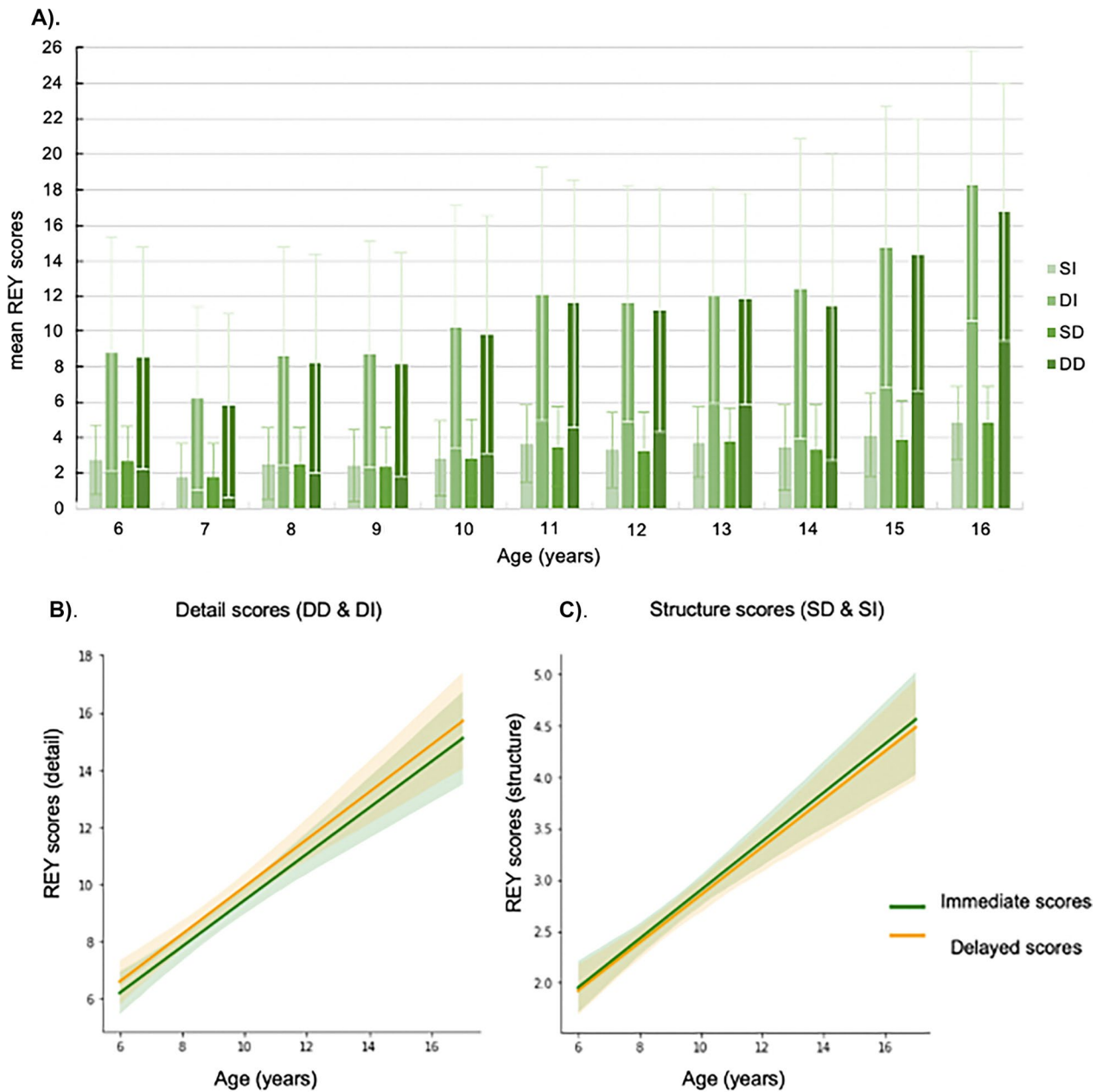


Fig. 1 A Bar plots showing RCFT scores in different age groups (the residual bars denote standard error of mean RCFT scores); B, C Plots presenting the positive relationships between RCFT scores and ages (the shaded area represents the 95% confidence interval of the regression)

Gene-based analysis identified a gene Rab11-family interacting protein one (*RAB11FIP1*) significantly associated with DD score ($P = 1.96E-06$, $P_{adj} = 0.036$).

Furthermore, in order to detect the genetic interaction networks between these four indexes, we constructed the protein networks connected by the mapped candidate genes (Fig. 2A). Both distinctive and common parts in the network were highlighted. Gene *TCL1B* and *TCL1A* were the central hub protein shared by DD, DI, and SI, and

interacts with genes involved in DI, SD, and SI (*FHDC1*, *ADAMTSL1*, *PARM1*, *CERS4*, *CDKL2*, *ZSCAN16*, *CREB1*). Genes of zinc protein family were also highlighted as top hub shared by DD and DI (*ZSCAN16*, *ZSCAN31*).

Candidate pathway analyses

We identified two pathways significantly involved in the RCFT. The forebrain neuron fate commitment

Table 2 Nominal significant loci associated with four RCFT scores

SNP	CHR	BP	A1	Beta	P-value	Mapped genes (location)	Mapped genes (eQTL and HiC)
REYDD							
rs56111147	14	96,153,765	C	-2.368	1.34E-06	TCL1B	TCL1A, TCL6 (HiC), TCL1B (eQTL)
rs277785	8	94,335,268	A	1.36	4.12E-06	LOC107986956	C8orf87 (Hi-C)
rs141358499	6	28,803,174	T	2.914	6.25E-06	NA	ZSCAN31, ZNF603P, ZSCAN8 (eQTL & HiC), AL022393.9, ZSCAN16 (HiC)
REYDI							
rs56111147	14	96,153,765	C	-2.656	1.25E-07	TCL1B	TCL1A, TCL6 (HiC), TCL1B (eQTL)
rs150898617	6	28,834,324	A	2.769	9.97E-07	RPL13P	ZSCAN31, ZNF192P1, ZNF602P, ZSCAN16 (eQTL); RPSAP2, ZNF311, RN7SL471P (HiC)
rs637487	1	191,459,085	A	-1.58	1.03E-06	NA	NA
rs857125	1	57,205,340	C	1.843	1.70E-06	C1orf168	C1orf168, PRKAA2 (Hi-C)
rs7667462	4	153,841,204	A	1.293	4.68E-06	FHDC1	ARFIP1 (eQTL)
rs4394025	4	76,497,433	C	-2.193	5.73E-06	NA	G3BP2, CDKL2 (eQTL & HiC); C4orf26, PARM1, RCHY1, THAP6, SO1 (HiC)
REYSD							
rs7594919	2	207,999,571	C	-0.648	3.29E-06	KLF7	KLF7, MIR2355 (HiC)
rs12981571	19	8,175,595	C	0.133	3.50E-06	FBN3	FBN3, CCL25, CERS4, ELAVL1 (HiC)
rs2778915	9	101,385,524	C	0.484	7.41E-06	GABBR2	GABBR2 (HiC)
rs12686018	9	18,879,776	A	-0.565	7.59E-06	ADAMTSL1	NA
rs72909972	2	157,109,471	C	0.505	9.65E-06	LINC01876	NR4A2
REYSI							
rs4932303	15	90,752,952	C	1.030	1.83E-06	SEMA4B	CIB1, SEMA4B (HiC & eQTL), GABARAPL3, GDPGP1, IDH2, NGRN (HiC), ZNF774 (eQTL)
rs12629965	3	128,422,658	A	-0.461	3.99E-06	NA	RPN1, POU5F1P6 (eQTL)
rs62188624	2	208,017,033	A	-0.651	4.18E-06	KLF7	KLF7, CREB1 (HiC)
rs56111147	14	96,153,765	C	-0.785	5.89E-06	TCL1B	TCL1A, TCL6 (HiC), TCL1B (eQTL)
rs2826536	21	22,187,947	C	0.415	6.29E-06	NA	LINC00320, NCAM2 (HiC)
rs4472720	1	187,613,231	G	-0.760	7.01E-06	NA	NA
rs12981571	19	8,175,595	C	0.593	7.40E-06	FBN3	FBN3, CCL25, CERS4, ELAVL1 (HiC)
rs17178718	17	5,551,690	C	0.812	7.64E-06	NA	NLRP1 (eQTL)
rs2761312	10	95,052,262	C	-0.731	7.83E-06	NA	MYOF (sQTL)
rs2088308	3	82,839,698	A	-0.432	8.1E-06	NA	NA
rs2705168	12	48,959,389	G	0.512	9.29E-06	LALBA	LALBA (HiC)
rs7071815	10	133,871,035	G	0.479	9.65E-06	JAKMIP3	JAKMIP3 (HiC & eQTL)

pathway was enriched in DD ($P = 4.78E-04$, $P_{adj} = 0.025$), and the dopamine transport pathway was enriched in SD ($P = 5.90E-04$, $P_{adj} = 0.031$).

Although no pathways associated with DI and SI scores passed the multiple test correction, forebrain neuron fate commitment and dopamine transport were implied to be potentially relevant to DI ($P = 1.16E-03$, $2.55E-03$); dopamine transport, adenylate cyclase inhibiting dopamine receptor signaling pathway and forebrain neuron differentiation potentially enriched in SI ($P = 2.16E-03$, $4.73E-03$, $7.62E-03$) (Table 3).

Polygenic risk score

A significant relationship was observed between DD and ADHD PRS scores, with an uncorrected P value of 0.0025, and an empirical P value of 0.035 (Fig. 2B). Although potential relationships between other RCFT scores and PRS were suggested, however, failed to pass the permutation test. The correlation heatmap was shown in the Fig. 2C.

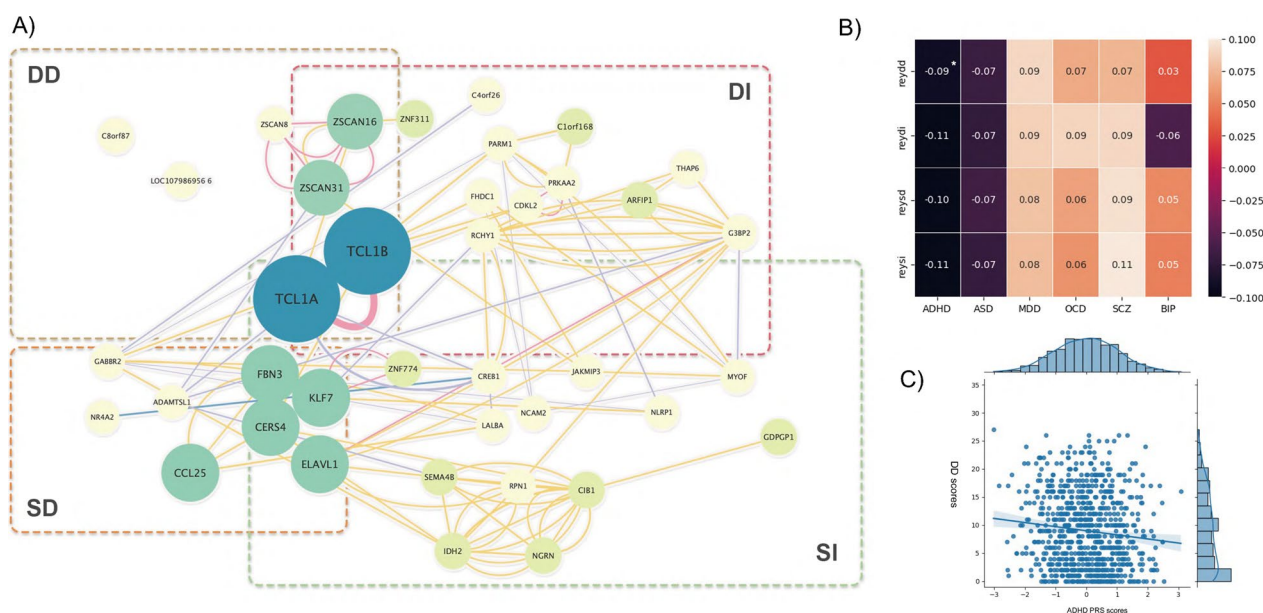


Fig. 2 Results of network and polygenic risk score analyses. **A** Gene interaction networks. Nodes and edges were constructed using relevant genes and gene interactions detected by GeneMANIA. Genes involved in four indexes exhibited a cooperative pattern, and TCL1A and TCL1B were identified as overlap nodes for three indexes (DD, DI, SI). Node size was determined by $-\log P$ (single-marker based P value), with sizes doubling if SNPs were involved in more than one index. Edges were constructed based on correlations between genes, with line width indicating the strength of correlation; **B** correlation heatmap between four RCFT scores and PRS scores for five psychiatric disorders. White asterisk denotes significant correlations (empirical P value less than 0.05); **C** Scatter plots for ADHD PRS scores and REY-DD, significant negative relationships were revealed

Discussion

The present study employed wide-range genetic analyses to explore the genetic basis underlying VSWM in ADHD. Although no SNP reached the genome wide significance, following the previous evidence demonstrated that missing heritability could be explained by the SNPs far below the genome-wide significance [28], we investigated the nominal significant SNPs ($P < 1E-05$) and highlighted a joint modulation pattern implemented by ocular and neural genes. And a differential pattern under four indexes might exist, with oculus related genes were implied to be more involved and neural system related genes less involved in detail scores compared with immediate scores. Gene-based analysis identified a significant brain-expressed gene *RAB11FIP1* (UniProt & lifeMap Discovery), which is critical for several neurodevelopmental process and visual pathways, associated with DD score. Dopaminergic circuit and forebrain development were suggested to be involved in SD and DD, respectively. Shared genetic basis between ADHD and VSWM were indicated, as the current study found the involvement of ADHD-related genes underlying VSWM and significant relationship between ADHD PRS and DD scores.

- (1) Ocular and neural system related genes jointly modulate VSWM.

Working memory is a complex and intricate system [69]. Neurobiological studies found that VSWM mainly includes two stages: (1) Visual perception, during which a set of physical signals enter the visual system and the brain interprets the electromagnetic signals and produces “a percept” or interpretation of the physical reality. In this process, neurons in the visual pathway, posterior early sensory and association areas are involved; (2) mnemonic representation, i.e., the brain, mainly PFC produces and maintains a mental representation of a percept when unavailable to the senses [70–72] The above findings from neurobiological studies suggested that the visual organ, the visual pathway, and the brain (mainly frontal lobe) are the basic biological structure underlying VSWM.

In line with previous knowledge, the current study provided further evidence that ocular and neural genes jointly modulate visual-spatial working memory through a comprehensive set of genetic analyses. Using GWAS method ($P < 1e-05$) (Table 2), we found that most relevant genes are brain-expressed (GTEx v8), and several genes are related to neurodevelopmental process and psychiatric disorders (Zinc finger family coding genes, *C8orf87*, *RPL13P*, *G3BP2*, *GABBR2*, *LINC01876*, *SEMA4B*, *RPNI* [73–85]); Meanwhile, multiple genes were found to be involved in the ocular system, with gene

Table 3 Top 5 enriched gene ontology (GO) pathway in four indexes

GO pathway	N gene	Beta	SE	P
REYDD				
Forebrain neuron fate commitment	9	1.1369	0.3441	4.78E-04*
Dopamine transport	47	0.20113	0.13196	6.37E-02
Wnt signaling pathway involved in midbrain dopaminergic neuron differentiation	11	0.39499	0.29188	8.80E-02
Midbrain dopaminergic neuron differentiation	16	0.29743	0.24711	1.14E-01
Regulation of dopamine uptake involved in synaptic transmission	7	0.33785	0.29334	1.25E-01
REYDI				
Forebrain neuron fate commitment	9	1.0519	0.34518	1.16E-03
Dopamine transport	47	0.37079	0.13236	2.55E-03
Forebrain morphogenesis	11	0.63099	0.30332	1.88E-02
Synaptic transmission dopaminergic	28	0.28778	0.14888	2.66E-02
Adenylate cyclase inhibiting dopamine receptor signaling pathway	8	0.68815	0.35835	2.74E-02
REYSD				
Dopamine transport	47	0.43833	0.1351	5.90E-04*
Forebrain neuron fate commitment	9	0.97901	0.35241	2.74E-03
Dopamine secretion	36	0.37745	0.16311	1.03E-02
Forebrain morphogenesis	11	0.58913	0.30966	2.86E-02
Forebrain regionalization	21	0.37972	0.22967	4.91E-02
REYSI				
Dopamine transport	47	0.3859	0.13521	2.16E-03
Adenylate cyclase inhibiting dopamine receptor signaling pathway	8	0.95016	0.36607	4.73E-03
Regulation of dopamine uptake involved in synaptic transmission	7	0.73861	0.30058	7.00E-03
Forebrain neuron differentiation	46	0.37687	0.15529	7.62E-03
Forebrain neuron fate commitment	9	0.80482	0.3527	1.13E-02

*Statistical significance with P-value < 9.43E-04

NLRP1 enhancing in Muller glia cells, gene *NR4A2* and gene *IDH2* over-expressing in the eye (LifeMap), and genes *TCL1B*, *TCL1A*, *TCL6*, *KLF7*, *FBN3*, *C1orf168*, *ADAMTSL1*, *MYOF*, *SEMA4B*, *CIB1*, *CREB1*, *CERS4* and *NLRP1* being involved in eye diseases and eye measurements, such as myopia [68], [86–93]glaucoma [88, 94], retinopathy [95], pinguecula [96], uveitis [97], corneal resistance factor, exploratory eye movement [86], and intraocular pressure measurement [87, 98].

Moreover, our findings suggested that portions of ocular genes and neural genes underlying the four indexes might vary. Compared with delayed recall, genes underlying immediate recall might be slightly more related to the visual system and less related to the neural system (Fig. 2A). *KLF7*, *FBN3*, *SEMA4B*, *CIB1*, *NLRP1*, *NR4A2* and *MYOF*, which were suggested only in immediate recall, were associated with visual system. However, in delayed recall task, only *TCLs* (*TCL1A*, *TCL1B*, *TCL6*), which also related to immediate recall (Table 3), and *C1orf168* were involved in visual function.

The results of gene-based analysis further support the current findings from GWAS analysis. Specifically, we

identified an association between DD scores and the *RAB11FIP1* gene, which was involved in both ocular and neural processes. *RAB11FIP1* is over-expressed in brain, encodes one of the Rab11-family interacting proteins (Rab11-FIPs), which plays a crucial role in the Rab-11 mediated recycling of vesicles. Proteins in the Rab11-FIPs family are known to modulate various neurodevelopmental processes, such as dendritic arborization, neurite pruning, synaptic plasticity, and spatial memory formation [99, 100]. Moreover, previous evidence indicated that these proteins are also involved in the visual system, as they have been implicated in retina neurogenesis [101, 102], photoreceptor cells development and maintenance [103, 104].

(2) Shared genetic basics between ADHD and VSWM.

The current studies identified genes shared by VSWM and ADHD, including *C8orf87* (DD) [105], *ZSCAN31* (DD, DI) [77, 83], *RPL13P* (DI) [85], *FBN3* (SD, SI) [74], and *LINC01876* (SD) [81, 83]. *C8orf87* was identified in a meta-analysis of ADHD GWAS studies [105]. *ZSCAN31*,

a member of Zinc finger protein family, encodes a protein containing multiple C2H2-type zinc finger motifs that are critical for neurodevelopment [73, 77]. Evidence found that *ZSCAN31* might underlie several neurodevelopmental disorders, including ADHD, ASD, Tourette syndrome, and SCZ [82, 83]. *FBN3* encodes a member of the fibrillin protein family. Previous GWAS analysis have indicated associations between *FBN3* and ADHD, brain morphology [74, 106].

Furthermore, our PRS analyses revealed ADHD PRS significantly predicted DD scores, providing additional evidence for a shared genetic basis between ADHD and short-term VSWM. Relationships between PRS and other three indexes failed to pass the permutation test, which might suggest the validity of DD, but not other indexes, as a neuropsychological endophenotype for ADHD. And this result was not surprising, because the delayed recall was one of the most consistent impaired functions reported in ADHD during RCFT task, and DD was supposed to demand the most WM load, able to reflect both encoding, maintenance, retrieval, organization, local and global processing [10, 14–16]. Our findings showed consistency with previous investigations found genetic correlations between ADHD and WM function [29, 107].

(3) Shared genetic basis between different part of VSWM.

Notably, one potentially shared genetic locus between DD, DI, and SI is rs56111147 located within the *TCL1B* gene, which encodes a T-Cell Leukemia/Lymphoma-1 family protein. In addition, the Hi-C data suggested that a chromatin loop can form between the genomic region (chr14:96,016,337–96,026,337, hg19) where rs56111147 is located and the promoter of *TCL1A* and *TCL6* (chr14:96,186,337–96,196,337, hg19). Although evidence mainly focused on the involvement of *TCLs* in hematological diseases and cancers, a previous large-scale GWAS ($n=542,934$) study identified associations between myopia and *TCLs* [68]. Further researches need to be done to fully understand the role of *TCLs* play in VSWM.

Genes *FBN3* and *KLF7* were also shared in structure scores, i.e., SD and SI. *FBN3* encodes a member of the fibrillin protein family, mainly localized to extracellular microfibrils of developing skeletal elements, and responsible to Weill–Marchesani Syndrome and Marfan syndrome. Evidence also suggested its expression in the brain (UniProt/SwissProt) [108]. Although previous studies have not yet clarified the function *FBN3* plays in nervous system, GWAS studies identified associations between *FBN3* and ADHD, brain morphology, which implied its role in NDDs by altering brain

development. *KLF7* encodes kruppel-like transcriptional regulator family, which regulates cell proliferation, differentiation, survival and contains three C2H2 zinc fingers at the C-terminus that mediate binding to GC-rich sites. *KLF7* plays a critical role in neuronal morphogenesis and survival of sensory neurons, and represses the corneal epithelium differentiation [76]. *KLF7* are also found to be associated with several psychiatric disorders, including ASD [109, 110], MDD [111] and sleep problems [112, 113]. A previous study reported that knockdowning *KLF7* in human brain organoids caused dysregulation of 517 ASD risk genes. Moreover, an increase of *KLF7* in the neural system in *KLF7*± adult mice significantly rescued ASD symptoms and the expression of majority of dysregulated ASD genes [110]. According to previous literatures, *KLF7* might provide protective effects to the brain through regulating the neural axon plasticity and activation of the JAK2/STAT3 signaling pathway [114, 115]. While there is no research on the potential role *KLF7* plays in VSWM or ADHD, our results encourage future studies.

(4) Forebrain commitment and dopamine transport are involved with VSWM.

The current study identified that forebrain neuron fate commitment and dopamine transport were significantly associated with DD and SD, respectively. Forebrain neuron fate commitment refers to the process in which the developmental fate of a cell in frontal lobe becomes restricted, which mostly occurs prenatally [116, 117]. Studies have demonstrated that disturbances in neural differentiation have profound effects on brain development and function, which might contribute to psychiatric disorders and cognitive deficits in later life through a variety of mechanisms, including aberrant neural migration, impaired synaptogenesis, and disruptions in neurotransmitter systems, et. al. Of particular interest are the neurotransmitter systems, where disruptions in the expression of genes in this pathway, including *PAX6*, *BCL11B*, *GATA2*, *ASCL1*, *TBL1*, *NKX2.1* could result in abnormal GABAergic, dopaminergic, and glutamatergic neuron development [118–124], and are associated with cognitive deficits [122, 125–128]. A possible underlying pathophysiological pathway is that the relevant genes might affect the excitatory/inhibitory balance [122–124], which is also considered as mechanisms in most psychiatry disorders including ADHD [129–131]

To conclude, our results indicated an early onset of altered neural substrates occurred during neuronal differentiation underlying VSWM and further emphasized the involvement of dopaminergic circuit.

Our study should be interpreted in light of some limitations. Firstly, we solely utilized the RCFT to evaluate VSWM. As previous studies have demonstrated, the RCFT is more sensitive to active WM processes [132]. Besides, EF is intensively required in RCFT task, which might be a confounding factor [12]. Therefore, future studies are encouraged to incorporate multiple VSWM tests to provide a more comprehensive assessment. Secondly, although we have performed interaction analyses to explore potential confounding effects caused by age, it remains difficult to fully address these effects. Future studies should take this issue into consideration through subgroup analyses or other methods with a larger sample size to provide more comprehensive insights.

It is worth noting that, as highlighted by previous findings, complex traits are often influenced by thousands or more genetic variants that exert their effects cumulatively. The "nominal" variants are believed to contribute a considerable proportion of the overall heritability [28, 133]. Thus, although no significant variants were detected by the current analysis, the suggestive variants might still provide further insights and lay a foundation for future studies in this area.

Conclusion

This study represents a genome-wide association study of VSWM, in which several genes, including *TCL1B*, *KLF7*, and *FBN3*, were identified as potentially related to VSWM. In addition, the brain-expressed gene *RAB11FIP1* was found to be significantly associated with DD. The results of polygenic risk score analyses provided evidence of shared genetic underpinnings between ADHD and VSWM, shedding light on the genetic basis of these conditions and potentially informing clinical practice in the future.

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Author contributions

YZ and YZ analyzed the data and wrote the draft. LY conceived the project and supervised the work. WC participated in data curation and data analysis. SC, QC, and YW participated in the conceptualization of the project and improved the written.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Ethical approval has been obtained from by the ethic commitment in Peking University Sixth hospital. Informed written consents were obtained from the parents of all children or from the participants who were over 8 years old.

Consent for publication

All the authors have approved the publication.

Competing interests

The authors declare no conflict of interest.

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