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Novel Genes Associated With Working Memory Are Identified by Combining Connectome, Transcriptome, and Genome

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ABSTRACT

Working memory (WM) plays a crucial role in human cognition. Previous candidate and genome-wide association studies have reported many genetic variations associated with WM. However, little research has examined genetic basis of WM by using transcriptome, even though it reflects gene function more directly than does the genome. Here we propose a new approach to exploring the genetic mechanisms of WM by integrating connectome, transcriptome, and genome data in a high-quality dataset comprising 481 Chinese healthy adults. First, relevance vector regression was used to define WM-related brain regions. Second, genes differentially expressed within these regions were identified using the Allen Human Brain Atlas (AHBA) dataset. Finally, two independent datasets were used to validate these genes' contributions to WM. With this method, we identified 24 novel genes and 20 of them were confirmed in the large-scale datasets of ABCD and UK Biobank. These novel genes were enriched in the cellular component of collagen-containing extracellular matrix and the CCL18 signaling pathway. Our method offers an effective approach to integrating multimodal gene discovery and demonstrates the superiority of expression data. This new method and the newly identified genes deserve more attention in the future.

1 | Introduction

Working memory (WM) is a neurocognitive system dedicated to the maintenance and storage of short-term information (Baddeley 2003; Ma, Husain, and Bays 2014), in the absence of sensory input (Eriksson et al. 2015). WM is the basis for successful execution of complex behaviors in various cognitive domains, which makes it vital for daily activities (D'Esposito and Postle 2015). The importance of WM functioning becomes apparent when taking an individual differences perspective: Research has demonstrated that WM capacity is a strong predictor of educational attainment (Alloway and Alloway 2010; Lee and Bull 2016; Mulder, Pitchford, and Marlow 2010). Furthermore, impairments in WM are symptomatic of several psychiatric and neurological disorders, such as Alzheimer's disease (Kumar et al. 2017), attention-deficit hyperactivity disorder (Patros et al. 2015), schizophrenia (Becske et al. 2022), and bipolar disorder (Peckham, Johnson, and Swerdlow 2019). Understanding

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the origins of individual differences in WM is therefore of pivotal interest. Previous research has attempted to explain these differences from both genetic and neural perspectives. In the present work, we build upon this foundation to further explore the genetic and neural underpinnings of individual variability in WM.

WM shows a moderate to high degree of heritability and many associated genes have been identified (He et al. 2021; Vogler et al. 2014). For example, *ZNF804A* (Nicodemus et al. 2014), *BIN1*(X. Zhang et al. 2015), *SLC12A5* (Gregory et al. 2019), and an interaction of *SPON1* and *APOE* (Liu et al. 2018) have been reported to contribute to WM performance as well as brain activation during WM tasks. Genome-Wide Association Studies (GWAS) have also identified many other genes such as *SCN1A* (Papassotiropoulos et al. 2011) and *EPHX2* (Zhang et al. 2022). An earlier review of GWAS on WM concluded that, although each study emphasized different genes, all of them are neuronal excitability-related genes, either related to ion-gated channels or to prefrontal dopamine activity (Knowles et al. 2014).

The neural mechanisms responsible for individual differences in WM have been extensively researched. Despite the considerable body of research reporting brain regions activated during WM tasks, which primarily include the frontal and parietal cortex, insula, premotor and supplementary motor areas, and basal ganglia (Christophel et al. 2017; Eriksson et al. 2015; Miller, Lundqvist, and Bastos 2018; Van Ede and Nobre 2023), the discovery of neuroimaging biomarkers is shifting away from traditional univariate brain mapping methods toward the adoption of multivariate predictive models. This shift provides an exciting opportunity to elucidate the intricacies of the human brain at the individual subject level (Sui et al. 2020). Connectomes, representing the whole brain's functional connectivity, are considered as "fingerprint" of the brain (Finn et al. 2015). Despite the fact that previous research has mostly used resting-state functional connectomes (Avery et al. 2020; Jiang et al. 2020; Pläschke et al. 2020; Zhang et al. 2020), a series of studies indicated that using task-based FCs or the integration of multiple modalities may confer greater predictive power and restingstate data may not be the best choice to predict cognitive traits (Finn 2017; Greene et al. 2018; Jiang et al. 2020), providing a better view in discovery of biomarkers (Finn 2017).

Despite the discovery of some possible mechanisms for individual differences in WM from the perspectives of brain and genetics, there is still a huge gap in our understanding of the relation between genotype and phenotype (here WM). That is, how do differences in genotype contribute to differences in phenotype, which in turn affect the brain, leading to variations in WM performance? Gene transcriptome and brain connectome have been proposed to help fill this gap (Fornito, Arnatkevičiūtė, and Fulcher 2019). Transcriptome, which reflects gene expression levels, is more directly connected to phenotype as compared to genotype. The Allen Human Brain Atlas (AHBA), a publicly available expression dataset for more than 20,000 genes across 3702 distinct brain tissues taken from six donors (Arnatkevičiūtė, Fulcher, and Fornito 2019; Markello et al. 2021), has been used successfully to reveal transcriptome-brain connectome associations (Arnatkeviciute et al. 2021; Park et al. 2021; Shafiei et al. 2022; Xie et al. 2022; Xu et al. 2022). It is very likely that using transcriptome may

identify WM-related genes that previous genotype association studies had missed.

The current study aimed to explore the underlying neural biomarkers of WM by examining individual differences in WM performance and identifying related genes. The study first identified activity and connectivity features that predicted individual differences in WM performance and mapped these features back onto brain regions to distinguish WM-related regions from non-WMrelated regions. Next, transcriptome analysis was used to find differentially expressed genes, which were then validated in datasets from the Adolescent Brain Cognitive Development (ABCD) and UKB studies to confirm their roles in individual differences in WM performance and executive control. By leveraging individual differences, this approach not only aids in more precisely identifying the neural signatures and genes associated with WM but also elucidates how gene expression influences brain function and, consequently, WM performance. This method offers advantages over traditional WM network identification techniques, as it more directly links genes to individual WM performance.

We proposed to identify novel WM-related genes with transcriptome and connectome using the following three-step procedure (Figure 1). First, we identified WM-related brain networks by combining task-based connectivity and task activation using a machine learning method based on relevance vector regression (RVR) (Tipping 2001). Second, we identified genes differentially expressed in these regions with AHBA transcriptome data. Finally, we confirmed the genes' effects by genotype-phenotype association in two independent samples.

2 | Method

2.1 | Step 1. Identifying WM-Related Brain Networks

2.1.1 | Participants

Participants were 481 healthy Chinese college students recruited from Beijing, China. Fifteen of them were excluded from analysis due to head movement of more than 3 mm during scanning and 20 were excluded due to poor-quality structural scans. This resulted in a final sample of 446 for brain imaging analysis (220 males and 226 females, mean age = 21.5 years, and SD = 2.3 years). All participants reported no history of psychiatric diseases, head injury, stroke, or seizure. This experiment was approved by the Institutional Review Board (IRB) of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University. Written informed consent was obtained from each participant after a complete description of the study procedures.

2.1.2 | WM Measurement

Participants performed an n-back task in the scanner. In this task, a sequence of numbers was presented one by one on the screen center. Each number was shown for 0.5 s followed by a 1.5 s blank. The experiment included two runs of the same four conditions. In the 0-back condition, participants were asked to judge whether the current number was 7. In the 1/2/3-back conditions, participants



FIGURE 1 | Flowchart of this study.

were required to decide whether the current number was the same as the one presented 1/2/3 items earlier. Each condition included 4 blocks, presented in a Latin square order, resulting in 16 blocks per run. For each block, a 4-s instruction was shown first, followed by a sequence of 12 numbers. Participants had to respond according to the instructions by pressing keys. The overall accuracy of the 1/2/3-back conditions was used as the index of WM performance. Before the experiment, subjects practiced the task to make sure they understood the task requirements.

2.1.3 | MRI Data Acquisition

Neuroimage data were collected on a 3.0T Siemens MRI Trio scanner at the Brain Imaging Center of Beijing Normal University. A single-shot T2*-weighted gradient-echo EPI sequence was used for functional imaging acquisition with the following parameters: TR = 2000 ms; TE = 25 ms; flip angle = 90°; FOV = 192 × 192 mm; 64 × 64 matrix size; 41 transversal slices; slice thickness = 3 mm. Functional images were scanned for the two runs of the n-back task (described above).

Anatomical MRI was acquired for normalization purpose using a T1-weighted, three-dimensional, gradient-echo pulse sequence. Parameters for this sequence were as follows: TR=2530ms; TE=3.39ms; flip angle=7°, field of view= 256×256 mm, matrix= 256×256 , and slice thickness=1.33 mm. One hundred and forty-four sagittal slices were acquired to provide a high-resolution structural image of the whole brain.

2.1.4 | MRI Data Analysis

Functional imaging data were preprocessed using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/) implemented

in MATLAB R2018b (MathWorks). Images were first slice-time corrected to the middle slice of acquisition and realigned to the first volume of each run. A mean image was generated from the realigned series and coregistered to the structural image. Structural images were segmented using DARTEL and a population-specific template was created. This template was used to normalize functional and structural images to the MNI template. The functional images were smoothed with an isotropic 8 mm full-width-half-maximum (FWHM) Gaussian filter. Intrinsic autocorrelations were accounted for by AR (1) and low-frequency drifts were removed via high-pass filter (time constant 128 s).

The task fMRI data were used to generate WM-related brain activation map using GLM. Volumes of the 0-back condition were not explicitly modeled and therefore were considered as the implicit baseline. Volumes of the 1-/2-/3-back conditions and the instructions were separately modeled using boxcar reference waveform convolved with a canonical hemodynamic response function. The six head movement variables were used as covariates. Contrast was specified as the 1-/2--/3-back conditions in contrast to the baseline (0-back). This contrast was used for group analysis, and activation regions were identified with a voxel-level FWE correction of p < 0.05.

The fMRI data were also used to construct FC. The whole brain was parcellated into 210 cortical regions and 36 subcortical regions based on the Human Brainnetome Atlas (Fan et al. 2016). For each region, the time series was calculated by averaging the blood oxygenation level-dependent (BOLD) time courses of all the voxels in it. The 1/2/3-back blocks were concatenated for task fMRI (i.e., excluding the 0-back and instruction blocks), and the time course was shifted forward by three TRs (6s) to account for hemodynamic lag (Eryilmaz et al. 2020; Kardan et al. 2022). For each participant, a 246×246 Pearson's correlation matrix between the time courses of all regions was computed for task fMRI, and the correlations were then Fisher transformed to z scores.

We used RVR to identify WM-related brain regions. Both taskevoked brain activation and FC matrix were used as features since integrating multiple data modalities can improve RVR prediction (Jiang et al. 2020; Kardan et al. 2022) (Figure S1). To make task-activated brain regions consistent with FC brain regions, the significantly activated regions were overlaid to Human Brainnetome Atlas, and regions in the atlas with more than 50% overlap were defined as WM-related regions.

We used 10-fold cross-validation RVR as used by He et al. (2021). First, participants were randomly divided into 10 subsets, 9 of which were for training and the remaining one for testing. Second, each brain feature was correlated with performance on the n-back task (accuracy), and a threshold was set to identify significantly correlated features. In order to find the optimal threshold, six commonly used thresholds (p<0.05, p<0.01, p<0.005, p<0.001, p<0.0005, and p < 0.0001) were tested and the one with best prediction was selected. Third, a regression model was constructed utilizing RVR to align the chosen functional connectivity with WM performance within the training dataset. Then the model was applied to the testing set. These steps were repeated 10 times, with each subset used as testing set and yielding a predictive score for each participant. The whole procedure was repeated 20 times, and the resulting prediction scores were averaged as final prediction. The Pearson correlation (r) between this averaged prediction and actual n-back accuracy was used as prediction accuracy. Lastly, statistical significance of the prediction accuracy was estimated by 1000 times permutation (shuffling n-back accuracy across participants). The empirical p values were calculated as the proportion of permutated r values that were equal to or larger than the true r value.

RVR-identified features were used to define WM-related regions, that is, brain regions either connected by identified FC or activated by the WM task. Across the 20 times of the 10-fold crossvalidation (200 models in total), the features selected by each RVR model differed a little bit. To construct a consensus network, features appeared in most of the 200 models were retained (Shen et al. 2017). Results of the retained features that appeared in 190/180/170/160 models were compared. To better describe the network, we estimated enrichment fold of the regions within the subnetworks defined by (Yeo et al. 2011) as in previous studies (Feng et al. 2022). The enrichment fold was the ratio of the number of observed edges in the subnetwork to the expected number of edges. The expected number of edges was the total number of selected edges in the whole brain multiplied by the proportion of the total number of edges in the subnetwork to the total number of edges in the whole brain. The significance of enrichment fold was estimated by 10,000 permutations, that is, randomly drawing the same number of selected edges to form a null distribution.

2.2 | Step 2. Identifying Differentially Expressed Genes

AHBA gene expression data (https://human.brain-map. org; Hawrylycz et al. 2012), which included brain-wide geneexpression data from 6 post-mortem brains (1 female, ages 24.0~57.0, 42.50 +/- 13.38), was downloaded and processed using abagen toolbox (version 0.1.3; https://github.com/rmark ello/abagen; Markello et al. 2021; Arnatkevičiūtė, Fulcher, and Fornito 2019). We used the 246-region Brainnetome atlas to define brain regions and selected the "centroids" option to deal with brain regions that were not assigned any sample from any donor. For all other settings, we used the default (Markello et al. 2021). Specifically, the probe sequences were first mapped to their corresponding genes to verify probe-to-gene annotations. Next, probes that fell below background levels in a significant proportion of samples were filtered out. For genes with multiple probes, a representative probe was selected. Tissue samples were then assigned to specific parcellated brain regions. Normalization was performed to account for inter-donor differences in gene expression, ensuring that samples no longer segregated by donor in the principal component space. Finally, the most relevant genes were selected based on consistent expression patterns across donor brains. The processed data were then organized into a regionby-gene matrix for further analyses. Specific parameters can be found in the Supporting Information. This resulted in a matrix of expression levels of 15,633 genes within 246 brain regions.

The 246 brain regions were divided into two groups. The first group included 88 regions that were related to WM based on RVR results, that is, the regions appeared in more than 95% of all 200 models (See details above). The second group included the remaining 158 regions that were not related to WM based on the RVR results. A two-sample T test was then used to compare the expression levels of each gene between these two groups of regions. Genes with significant expression differences were identified as over- or under-expressed genes within the WM network. Permutation procedure was used to control multiple comparisons. To do the permutation, we first shuffled the labels of WM-related and WM-unrelated among brain regions and then ran the two-sample T-tests. This procedure was repeated 10,000 times to form a null distribution for over- or under-expression. The p value was calculated as the proportion of t-values in the positive (or negative) t-value distribution that were larger (or smaller) than the actual t-value. Genes with permutation p < 0.05 were identified as WM-related genes. To see how robust the results were, we repeated the analyses under different selection thresholds to define WM-related regions (90%, 85%, 80%, i.e., features identified by RVR as WM related in more than 180, 170, and 160 times of the 200 models). Genes consistently identified in different models were used as candidate WM-related genes for further confirmation in Step 3.

2.3 | Step 3. Confirming the Associations Between Identified Genes and WM

We used two independent samples (the ABCD Project and the UK Biobank) to confirm the genes identified in Step 2.

We first estimated the expression level of each gene for each participant in the ABCD project using MetaXcan (https://github.com/ hakyimlab/MetaXcan.git), and then associated the genes' expression levels with WM performance by conducting transcriptomewide association studies (Gamazon et al. 2015). Since it is impossible to take brain tissue from these participants to test the transcription level, MetaXcan takes two steps to estimate the transcription level.

First, genotype-transcription relationship was set up using other datasets. MetaXcan provided genotype-transcription relationships for all genes with 13 brain tissues from GTEX v8 database (Barbeira et al. 2021), calculated with MASHR-based method since it was biologically informed and performed better than other methods (Araujo et al. 2023). Second, genotype and WM performance data (NIH toolbox List Sorting WM task) were downloaded from the ABCD project under the permission of 13,109. Stringent quality control was applied to the genotype data: $R^2 > 0.8$, MAF >0.05, HWE>10E-7, and less than 10% missing, resulting in 8,546,049 SNPs. The genotype-transcription relationships from the first step were applied to ABCD genotype data to estimate gene expression levels of ABCD participants. The expression levels of all genes were then correlated to WM performance using Pearson correlation controlling for age and sex. This correlation of the identified genes was checked. Subjects without behavior data were excluded from the analysis. The analysis was repeated for each of the 13 GTEX brain tissue genotype-transcription relationships. We then compared genes identified in step 2 with published WM GWAS results. We examined a recent study that analyzed GWAS results for a common executive function (cEF) factor score derived from multiple tasks, including WM tasks such as pairs matching and backward digit span, among 427,037 individuals from the UK Biobank (Hatoum et al. 2023). The study provided MAGMA analysis results at the gene level. We cross-referenced our identified genes with all cEF-related gene-level MAGMA analysis results from their study to determine whether our genes exhibited significant associations. For validation, we employed a significance threshold of 0.05.

Finally, to gain deeper insights into the WM-related genes, we used the GENE2FUNC module in FUMA (https://fuma.ctglab.nl/) for gene ontology and gene set enrichment analysis. FUMA integrates data from various biological resources for functional annotation of GWAS results (Watanabe et al. 2017). We analyzed 24 WM-related genes in the FUMA platform, selecting all genes as background genes and setting the threshold for "Minimum overlapping genes with gene-sets" to greater than 2. Multiple comparison correction was performed using the Benjamini–Hochberg (FDR) method.

3 | Results

3.1 | WM Brain Networks

The N-back task activated vast brain regions in the bilateral frontal-parietal network, including superior frontal, middle frontal, precentral, supplementary motor area, insula, cingulate and paracingulate, putamen, superior parietal, supramarginal gyrus, and angular gyrus (Figure 2), consistent with the literature (Braun et al. 2015; Braunlich, Gomez-Lavin, and Seger 2015; Darki and Klingberg 2015; Marek and Dosenbach 2018). Overlaying these activation areas onto the Human Brainnetome Atlas resulted in 48 regions. Mean activation for each subject at each region was extracted and combined with FC for the following RVR analysis.

The RVR analyses revealed that for each of the feature-selecting thresholds, brain measurements were significantly associated with WM performance, r ranging from 0.172 to 0.198, with the strongest prediction achieved at the feature-selecting threshold of 0.001 (Table 1, Figure 3A).

The consensus brain network (features retained in 190 out of 200 models) from RVR consisted of 127 edges connecting 88 widely distributed cortical and subcortical areas (Figure 3B). The high-degree nodes were mainly located in the superior temporal gyrus, lateral occipital cortex, basal ganglia, parahippocampal gyrus, hippocampus, and insular gyrus. Enrichment fold of the regions within the subnetworks showed that these edges were enriched in the connections between the Ventral Attention Network and





the Limbic Network (4.978 folds, p < 0.0001), between the Visual Network and the Limbic Network (1.879 folds, p < 0.05), and between the Visual Network and the Dorsal Attention Network (1.628 folds, p = 0.0513) (Figure 3C). Since the threshold influenced the consensus network (i.e., lower threshold resulted in more regions), we also tested lower thresholds (i.e., 180, 170, 160 out of 200 models), the results are similar (Figure S2).

3.2 | Differentially Expressed Genes

The AHBA gene expression levels of 15,633 genes were compared between brain regions in and out of the consensus brain networks identified above. With all four consensus networks (retained in 190/180/170/160 out of 200 models), 146 unique genes were identified as over- or underexpressed in the WM network (Table S1). Of them, two (COL18A1 and SPINK8) were identified by all four networks, and 22 were identified by three networks (Table S1). We considered these 24 genes as candidate genes to be confirmed by independent samples (Table 2). The results of the FUMA enrichment analysis showed that these genes are enriched in the collagen-containing extracellular matrix (p < 0.05, FDR correction). The extracellular matrix (ECM) surrounds brain cells, providing structural and functional support, and plays an important role in brain development and brain health (Soles et al. 2023). Additionally, these genes were also enriched in the CCL18 signaling pathway. Studies had found that CCL18 is a biomarker of inflammation and neurodegeneration in MS patients and may be associated with brain diseases (Ziliotto et al. 2018).

TABLE 1 | Prediction accuracy under the six different thresholds.

Threshold	r	p ^a	p _{permu} ^b
0.05	0.174	0.00022	0.002
0.01	0.172	0.00025	0.001
0.005	0.182	0.00011	0.004
0.001	0.198	0.00003	0.000
0.0005	0.180	0.00013	0.001
0.0001	0.181	0.00012	0.002

^aOriginal *p* values of the prediction.

 ^{b}p values obtained by the permutation tests.

3.3 | Genes Confirmed by Significant Association With WM Performance in Independent Samples

In the ABCD dataset, 18 out of the 24 genes showed significant associations between WM performance and the estimated gene expression level in at least one tissue (Table 2). After excluding brain tissues that were not involved in our WM network, validation results still included 17 genes (Table 2). Of note, the most robust genes identified above (*COL18A1* and *SPINK8*) also showed strong effects with expression level of multiple tissues. In the UK Biobank large sample GWAS, *CCL19*, *COL1A2*, *ELOVL7*, *IFI27*, *MAP7*, and *SLC2A1* showed significant associations with WM performance. Taken together, 20 of these genes were replicated in at least one of the two samples.

4 | Discussion

The current study used a novel approach to identify WM-related genes with gene expression data. We employed machine learning methods to identify features that might cause individual differences in WM performance. These features helped us define brain regions related to WM. By comparing the gene expression data of WM-related and unrelated brain regions in the AHBA, we identified 24 differentially expressed genes and confirmed that 20 of these genes were associated with WM performance in at least one of two independent samples. These results suggest that it may be productive to combine connectome, transcriptome, and genome to help identify novel genes related to a given phenotype.

First, as a confirmation, the brain regions our approach identified as supporting WM have often been reported in the WM literature. For example, the basal ganglia plays a crucial role in facilitating the selective filtering of pertinent information into WM (McNab and Klingberg 2008); the parahippocampal cortex functions as a WM buffer by actively preserving new information in a capacitydependent manner (Schon et al. 2016); the superior temporal gyrus plays a crucial role in WM maintenance (Park et al. 2011) and the repetition suppression effects caused by the repeated presentations of stimuli (Woodward et al. 2013); and the occipitoparietal network supports WM with the retention of stimuli in sensory and higher cortical regions (Johnson et al. 2017). The visual network is often involved in visual WM task (Lawrence et al. 2018); the ventral attention network is usually involved in differentiating WM load (Eryilmaz et al. 2020); and the dorsal attention network



FIGURE 3 | WM brain network identified by RVR. (A) Prediction accuracy; (B) selected connectivity by RVR; (C) selected connectivity was enriched in the connections among the Ventral Attention-Limbic-Visual-Dorsal Attention Networks.

TABLE 2	Confirmation of genes	' effect on WM in	independent	samples.
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AHBA identified	ABCD replicated ^a	ABCD replicated (WM network only) ^b	UKB replicated
COL18A1	COL18A1 (9)	COL18A1 (5)	_
SPINK8	SPINK8 (10)	SPINK8 (8)	_
A2M	A2M (6)	A2M (5)	_
APOL3	APOL3 (12)	APOL3 (7)	_
CAPS	CAPS (4)	CAPS (1)	_
CARD10	CARD10 (8)	CARD10 (5)	_
CCL19	CCL19 (8)	CCL19 (4)	CCL19
CLDN5	CLDN5 (4)	CLDN5 (4)	_
CLEC14A	_	_	_
COL1A2	COL1A2 (2)	COL1A2 (2)	COL1A2
ELOVL7	ELOVL7 (9)	ELOVL7 (5)	ELOVL7
FAM234A	FAM234A (9)	FAM234A (5)	_
GCN1	GCN1 (7)	GCN1 (5)	_
IFI27	_	_	IFI27
IL4R	IL4R (3)	IL4R (1)	_
KCNMB1	KCNMB1 (4)	KCNMB1 (3)	_
LATS2	LATS2 (3)	LATS2 (2)	_
MAP7	_	_	MAP7
MFAP4	MFAP4 (1)	MFAP4 (1)	_
PECAM1	_	_	_
PRX	PRX (12)	PRX (7)	_
SLC2A1	SLC2A1 (1)	_	SLC2A1
SNHG17	_	_	—
ZEB2	_	_	_

Note: All confirmed at p < 0.05.

^aThe number of replicated tissues are shown in brackets.

^bThese genes' effects on WM were replicated when we used expression data from brain tissues located in WM network only.

is linked to task-related, top-down attention control (Majerus et al. 2018). With increasing short-term memory load, the dorsal attention network is activated while the ventral attention network is deactivated (Majerus et al. 2012). Alzheimer's disease patients have been found to maintain ventral attention network activation under high cognitive load (Kurth et al. 2019). In sum, our results are consistent with the previously discovered WM network.

Second, by comparing expression levels of genes between brain regions in and out of the consensus WM network, we identified a number of over-/underexpressed genes. Because the threshold used to define the consensus network may influence the number of brain regions to be included in subsequent analyses, we tested four thresholds. Twenty-four genes were consistently identified. These results per se cannot lead to the conclusion that these genes are involved in WM, but they can serve as good WM candidate genes.

Finally, we confirmed that 20 of the genes were associated with WM in two independent datasets, showing that either their

genotype or estimated expression was significantly associated with WM performance. Compared to the UK Biobank dataset, the ABCD dataset demonstrated better replication performance despite its smaller sample size. This could be attributed to two factors. First, the ABCD data used expression data, which may provide a more direct approach on elucidating the role of genes in phenotypes. Additionally, although cEF and WM were closely related, there were still certain differences in their genetics. The specificity and commonality of genes among different cognitive components have been a worthwhile research topic, and further exploration in this area can be conducted in future studies. Although the functions of most of these genes are still unclear, some of them have been reported to be associated with cognition or diseases that are related to WM. We found that COL18A1 and SPINK8 were consistently related to WM under all four thresholds. COL18A1 is associated with a rare condition known as Knobloch's syndrome, whose key characteristic is developmental abnormalities in the brain, particularly defects in the occipital region (Caglayan et al. 2014). Research has also suggested a connection between COL18A1

and early-onset cognitive impairments (Najmabadi et al. 2011). Additionally, it is also associated with hippocampal volume, which is key to memory and serves as a biomarker for Alzheimer's disease (Melville et al. 2012). Similarly, studies in mice have found that *Spink8* is specifically expressed in the pyramidal cells of the hippocampus (Zeisel et al. 2015), linking *SPINK8* to memory. Interestingly, a large-scale GWAS study has identified two SNPs of *SPINK8* that are associated with educational attainment (Okbay et al. 2016, 2022). Considering the predictive role of WM in academic performance (Alloway and Alloway 2010; Nyroos and Wiklund-Hörnqvist 2012), this evidence may indirectly suggest a correlation between *SPINK8* and WM.

Some other genes identified in our study have also been implicated in WM. For instance, a previous study found a significant relationship between methylation of the *CLDN5* locus and changes in cognitive function, especially related to episodic and WM (Hüls et al. 2022). In a GWAS focusing on executive function, the *ELOVL7* gene was found to be related to WM (Donati, Dumontheil, and Meaburn 2019). The variations in *CARD10* have been correlated with the rate of hippocampal volume loss, suggesting its potential involvement in the neurodegenerative processes associated with Alzheimer's disease (Nho et al. 2013). *A2M* has been linked to early neural damage and disease progression in Alzheimer's disease (Dong et al. 2022; Varma et al. 2017). Furthermore, compared to healthy controls, the expression of *COL1A2* is downregulated in Alzheimer's disease patients (Vastrad and Vastrad 2021).

Some of the remaining genes identified in our study are closely linked to the functioning of the nervous system more generally. For instance, genetic variations in the *IL4R* gene may be related to the normal progression of childhood neurodevelopment (Clark et al. 2010). The *SLC2A1* gene encodes glucose transporter type 1, which is a crucial transporter protein involved in cellular glucose uptake across various tissues and is highly expressed in the brain (Vulturar et al. 2022). Mutations in the *SLC2A1* gene have been implicated in a wide range of neurological disorders (Wolking et al. 2014).

To summarize, we proposed a new three-step approach to exploring gene-phenotype association (i.e., defining a brain network, identifying differentially expressed genes, and confirming genephenotype association), and successfully identified some novel genes that are associated with WM. We used both genotype and gene expression data. Because gene expression can better reflect gene function, we believe that genes identified by expression data should have higher gene-based interpretability and tissue specificity for understanding the mechanisms than should those identified via GWAS (Mai et al. 2023). Indeed, we found that the identified novel genes were more likely to be confirmed by estimated gene expression (the ABCD replication sample) than the GWAS (the UK Biobank sample), suggesting that expression data can confirm novel genes that may have been missed by previous GWASs.

This study has several limitations. First, we used the AHBA dataset to identify differentially expressed genes in the brain. It is currently the best available database, but it has only six European donors, with only two providing data for the right hemisphere, which may limit their generalizability. However,

by estimating gene expression for each participant in the large ABCD sample and running TWAS analysis, we validated most of the genes identified by AHBA. Second, there are differences in sample characteristics such as ethnicity, age, and sex between our Chinese sample and the AHBA/ABCD/UKB samples, which may introduce population bias in the results. Further replication studies are needed for each type or subtype of population. Third, our confirmation datasets are limited and the gene-WM association we found is rather moderate. More studies are needed to confirm the contributions of these genes to WM and investigate the underlying biological mechanisms. Last but not least, the observed region-specific differences in gene expression may be influenced by other factors than WM. To mitigate these potential confounding effects, we employed a permutation test to control for potential confounding effects and verify the specificity of our results. Our TWAS analysis supports the relevance of differentially expressed genes to WM performance, reinforcing their functional significance in a separate population (ABCD cohort). Additionally, the GWAS-based validation in the UK Biobank based on Hatoum et al. (2023) lends further support to the role of these genes in cognitive performance. It is important to note that not all initially identified differentially expressed genes could be validated. This limitation could stem from inherent differences in gene function related to brain function, which may not directly translate to observable variations in WM performance. Alternatively, it may reflect the possibility that some genes identified in the differential gene expression analysis were nonspecific which warrants further investigation.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.