Schizophrenia

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Interaction between *BDNF* Val66Met polymorphism and mismatch negativity for working memory capacity in schizophrenia

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Both the brain-derived neurotrophic factor (*BDNF*) valine (Val)/methionine (Met) polymorphism and mismatch negativity (MMN) amplitude are reportedly linked to working memory impairments in schizophrenia. However, there is evident scarcity of research aimed at exploring the relationships among the three factors. In this secondary analysis of a randomized, controlled, double-blind trial, we investigated these relationships. The trial assessed the efficacy of transcranial direct current stimulation for enhancing working memory in clinically stable schizophrenia patients, who were randomly divided into three groups: dorsolateral prefrontal cortex stimulation, posterior parietal cortex stimulation, and sham stimulation groups. Transcranial direct current stimulation was administered concurrently with a working memory task over five days. We assessed the *BDNF* genotype, MMN amplitude, working memory capacity, and interference control subdomains. These assessments were conducted at baseline with 54 patients and followed up post-intervention with 48 patients. Compared to *BDNF* Met-carriers, Val homozygotes exhibited fewer positive and general symptoms and increased working memory capacity at baseline. A correlation between MMN amplitude and working memory capacity was noted only in *BDNF* Val homozygotes. The correlations were significantly different in the two *BDNF* genotype groups. Furthermore, in the intervention group that showed significant improvement in MMN amplitude, *BDNF* Val homozygotes exhibited greater enhancement in working memory capacity than Met-carriers. This study provides in vivo evidence for the interaction between MMN and *BDNF* Val/Met polymorphism for working memory capacity. As MMN has been considered a biomarker of N-methyl-D-aspartate receptor (NMDAR) function, these data shed light on the complex interactions between *BDNF* and NMDAR in terms of working memory in schizophrenia.

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INTRODUCTION

Mismatch negativity (MMN) is an event-related potential that reflects the brain's automatic attentional engagement in information processing. MMN is elicited by the presentation of infrequently occurring deviant stimuli interspersed within frequently occurring standard stimuli[1]. MMN is significantly impaired in schizophrenia, correlating closely with functional outcomes[2–7], and it is considered one of the most mature biomarkers for schizophrenia[8], providing a groundbreaking biological signpost for understanding and treating the disorder[9]. Additionally, MMN is a valid biomarker for N-methyl-D-aspartate receptor (NMDAR) function in schizophrenia[10]. Ketamine, an NMDAR antagonist, not only induces psychotic symptoms but also reduces MMN amplitude in healthy individuals[11]. Furthermore, MMN can serve as a biomarker for NMDAR-mediated improvements in negative symptoms[12] and auditory plasticity[13,14] in schizophrenia. Thus, it is crucial to understand the relationships of MMN amplitude with other behavioral phenotypes (e.g., cognitive functions) and influential factors, which may guide intervention trials for behavioral improvement.

Working memory serves as a fundamental element of executive function[15] and is identified as a central cognitive dysfunction in schizophrenia[16,17]. A study suggested that MMN amplitude mediated the influence of the glutamine-to-glutamate ratio on working memory in schizophrenia[18]; however, some studies could not identify a link between MMN amplitude and working memory in schizophrenia[19]. These discrepancies may be partly attributed to variations in the working memory assessment tools used. For working memory assessments, previous research typically used classic neuropsychological tests like the digit sequencing task[19]. However, cognitive neuroscience approaches offer a more comprehensive assessment of working memory subdomains, thus facilitating a more lucid understanding of the intrinsic mechanisms[20]. The change detection task is a recommended cognitive neuroscience approach for evaluating working memory capacity[21]. Its modified version can be used for assessing both capacity and interference control subdomains of working memory[22]. Therefore, using the modified change detection task may provide vital insights into the relationships of MMN amplitude with working memory capacity and interference control.

Working memory deficits are closely tied to NMDAR-mediated gamma oscillation anomalies in schizophrenia[16,23]. The NMDAR function is regulated by brain-derived neurotrophic factor (BDNF)[24], which is among the most extensively studied peripheral indicators associated with cognitive function in schizophrenia[25]. BDNF can increase the abundance of synaptic NMDAR[26] and reduce extrasynaptic NMDAR death signaling[27]. The Val66Met polymorphism in the *BDNF* gene results in a substitution of

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methionine (Met) for valine (Val) at the 66th codon, resulting in insufficient BDNF secretion[28]. Thus, the *BDNF* Val66Met polymorphism could cause NMDAR dysfunction and working memory impairments in schizophrenia[24,28]. Carriers of the *BDNF* Met/Met genotype exhibit disrupted NMDAR-dependent long-term potentiation and depression compared to wildtype controls, particularly in brain regions such as the hippocampus[29] and the medial prefrontal cortex[30]. In addition, research has shown that *BDNF* Val homozygotes have larger MMN amplitude than Met-carriers among musicians[31]. Thus far, there has been no investigation into the potential impact of the *BDNF* genotype on the correlation between working memory and MMN amplitude in patients with schizophrenia.

In a randomized, controlled, double-blind trial, we found that transcranial direct current stimulation (tDCS) targeting the posterior parietal cortex improved working memory and MMN amplitude in schizophrenia, compared to targeting the prefrontal cortex or sham stimulation[32]. In a secondary analysis of this trial, we analyzed data from baseline and post-intervention assessments to investigate the correlations of MMN amplitude with both working memory capacity and interference control in schizophrenia while considering the potential impact of the *BDNF* Val/Met polymorphism. Given that the *BDNF* Val/Met polymorphism may influence NMDAR-dependent long-term potentiation and depression[29,30], which are foundational for memory[33], we hypothesized that the relationship between MMN amplitude and working memory would be regulated by the *BDNF* Val/Met polymorphism.

MATERIALS AND METHODS

Participants

All participants were from a double-blind, three-arm, randomized trial of which the primary objective was to compare the therapeutic differences among tDCS paradigms (targeting the prefrontal cortex vs. targeting the posterior parietal cortex vs. sham stimulation) synchronous with cognitive tasks for working memory in patients with schizophrenia[32]. Each participant provided formal informed consent before the trial commencement. This study received approval from the Ethics Committee of Beijing Anding Hospital (No. 2020-70), and was registered in the Chinese Clinical Trial Registry (ChiCTR2000038961); the information was synced with the World Health Organization international clinical trials registry platform.

The eligible participants were schizophrenia outpatients or community-dwelling schizophrenia patients with impaired working memory. High-definition tDCS was conducted using a DC-Stimulator Plus (NeuroConn, Germany) equipped with a 4×1 wire adaptor (Equalizer Box, NeuroConn, Germany). For the prefrontal cortex, the central electrode was positioned at F3, surrounded by four electrodes at F7, Fz, Fp1, and FC3. For the posterior parietal cortex, the central electrode was placed at P3 with four surrounding electrodes at P7, Pz, O1, and CP3. For the two real stimulation groups, the electrode intensity was set to 2 mA for a duration of 20 min, with a 40-s ramp-up and ramp-down period. The sham stimulation mirrored this setup, but the actual stimulation duration was limited to 40 s. High-definition tDCS with a concurrent N-back task, was administered twice daily for five consecutive days, and assessments were conducted at baseline, week 1, and week 2.

The primary outcome of the clinical trial was the change in spatial span test scores at week 1 from baseline. Secondary outcomes encompassed changes in scores of the change detection task and other cognitive assessments. Additionally, MMN was collected as a biomarker. Among the initial 60 participants, 54 underwent testing for single-nucleotide polymorphisms, the findings of which were employed in the baseline analysis of this report (Supplemental Fig. 1). Prior analysis revealed that compared to the prefrontal cortex stimulation group and the sham stimulation group, the posterior parietal cortex stimulation group had significant improvement in MMN amplitude at week 1[32]. Consequently, the posterior parietal cortex stimulation group was considered as the group with notable MMN amplitude enhancement. The longitudinal data involving the change detection task served as the validation dataset in this study.

Clinical symptom and working memory assessments

Clinical symptoms were assessed according to the positive and negative syndrome scale (PANSS), which took approximately 30 minutes. Capacity and interference control subdomains of working memory were evaluated utilizing a modified change detection task[22], lasting about 40 min. In each trial, an arrow appeared initially, signaling participants to pay attention to the upcoming arrow-directed visual field. The task of the participants was to memorize the colors of all the squares (targets) within the arrow-directed field while ignoring the distracters and colors in the opposite field. After a retention interval, a test array prompted participants to recall if square colors had changed in the arrow-directed visual field. The task comprised four conditions: two targets without distracters, four targets without distracters, two targets with two distracters, and four targets with two distracters. Conditions were presented pseudo-randomly with two blocks for each condition, and each block comprised 80 trials. Changes in the test array occurred with a 50% probability (Fig. 1). To assess working memory capacity, Cowan's K was calculated as follows: Cowan's K = memory load × (the rate of change response when color change occurred - the rate of change response when no color change occurred)[34]. To assess interference control domain, filtering efficiency was computed as follows: filtering efficiency = Cowan's K in the absence of distracters - Cowan's K in the presence of distracters[22].

MMN paradigm

The MMN paradigm comprised 90% standard stimuli (50 ms, 675 trials) and 10% deviant stimuli (100 ms, 75 trials). MMN collection required approximately 12 min. Electroencephalographic recordings were obtained via a 128-channel high-density system from Electrical Geodesics, Inc., USA, operating at a 1000-Hz sampling rate and maintaining all electrode impedances under 50 kΩ. Participants focused on a "+" symbol while receiving auditory stimuli. Electroencephalograph data underwent high-pass filtering at 0.5 Hz, low-pass filtering at 30 Hz, and notch filtering between 48 Hz and 52 Hz to eliminate electrical interference. Continuous data were segmented into intervals from −100 ms to 500 ms, with the stimulus onset as the zero point. Replacement of bad electrodes and removal of bad segments were manually performed. Reference electrodes were set to the average reference, and artifacts were separated using independent component analysis. Segments exceeding ±100 μV in amplitude were removed. Electrode E6 (corresponding to the FCz in the 10–20 electroencephalograph system) was selected for analysis. The MMN waveform was obtained by deducting the waveform evoked by the standard stimuli from that evoked by the deviant stimuli. The amplitude minima between 140 ms and 240 ms were extracted as the MMN amplitude for each participant[35]. To ensure the stability of the findings, additional analyses were conducted based on two multi-site average clusters (electrodes 5, 6, 7, 12, 106; electrodes 5, 6, 7, 12, 13, 106, 112).

Genotyping

Whole blood was utilized for deoxyribonucleic acid extraction. The rs6265 locus sequence was detected for the *BDNF* Val66Met polymorphism. Genotype identification procedures involved

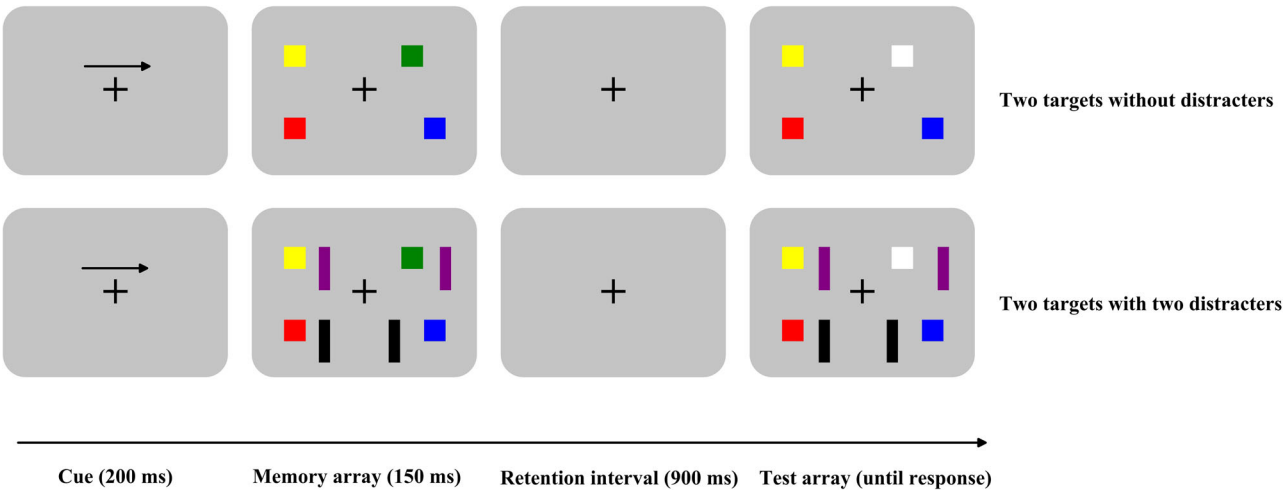

Fig. 1 Change detection task.

polymerase chain reaction amplification and subsequent agarose gel electrophoresis. Among the 54 samples, 17 had *BDNF* Val/Val, 15 had *BDNF* Val/Met, and 22 had *BDNF* Met/Met. Participants with Val/Met and Met/Met were combined as Met-carriers for subsequent analysis.

Statistical analysis

Statistical analyses were performed utilizing the SPSS 20.0 software package (SPSS Inc., Chicago, IL, USA). The distribution of data normality was verified through histogram analysis and the Shapiro–Wilk test. To determine whether genotype distributions diverged from the Hardy–Weinberg equilibrium, the Chi-square test and Fisher's exact test were employed. These tests, as well as the t-test, were applied to compare demographics, clinical characteristics, baseline working memory, and baseline MMN amplitude among genotype groups. Demographics and clinical characteristics that differed significantly among genotype groups were included as covariates in the covariance analysis. This controlled for potential influences on differences in baseline working memory and MMN amplitude across groups. Bonferroni corrections were implemented for multiple comparisons involving clinical symptoms, working memory capacity, and interference control.

Pearson correlation was used to assess the relationships of MMN amplitude with both working memory capacity and interference control in the entire sample and in specific genotype groups (*BDNF* Met-carriers and Val homozygotes) at baseline. Bonferroni corrections were adopted for capacity and interference control respectively. Additionally, the magnitude of these correlations was compared across genotype groups[36]. Furthermore, multiple linear regression was employed to examine the interaction effects between MMN amplitude and genotype in relation to working memory at baseline. In the multiple linear regression analysis, working memory served as the dependent variable, while the *BDNF* genotype, MMN amplitude, and their product were treated as independent variables. Gender, age, PANSS total score, and chlorpromazine equivalents were included as covariates. For working memory domains and genotypes with significant interaction results at baseline, the Fisher exact test and Welch analysis of variance were adopted to compare baseline characteristics and working memory enhancement across different genotype subgroups within the three intervention groups in the clinical trial. A *P*-value of less than 0.05 (two-sided) was set as the criterion for statistical significance.

RESULTS

Clinical characteristics in genotype groups at baseline

The distribution of the *BDNF* genotype exhibited no departure from the Hardy–Weinberg equilibrium ($\chi^2_2 = 5.662$, $P = 0.059$). Compared to *BDNF* Met-carriers, Val homozygotes showed significantly lower scores in PANSS positive symptoms ($t_{51} = 2.839$, $P = 0.006$), general symptoms ($t_{51} = 3.325$, $P = 0.002$), and total symptoms ($t_{52} = 2.789$, $P = 0.007$). These findings remained statistically significant even after Bonferroni corrections ($P < 0.05$). No significant disparity was observed in PANSS negative symptoms between the *BDNF* genotype groups ($t_{52} = 1.105$, $P = 0.274$) (Table 1).

MMN amplitude and working memory within *BDNF* genotypes at baseline

BDNF Val homozygotes demonstrated significantly higher working memory capacity under four target loads compared to Met-carriers ($t_{49} = -2.356$, $P = 0.023$), and this significance persisted after Bonferroni corrections ($P < 0.05$) (Fig. 2A). Significant differences were not observed between the *BDNF* genotype groups concerning interference control and MMN amplitude (Table 1) (Fig. 2B). The MMN results derived from two multi-site average clusters and single-site recordings were consistent. Using PANSS positive symptom, general symptom, and the total score as covariates, the covariance analysis revealed a significant difference in working memory capacity under four target loads between the groups ($F_1 = 5.153$, $P = 0.028$), with borderline significance noted after adjustment ($P = 0.056$).

MMN amplitude, genotypes, and working memory at baseline

In the entire sample, MMN amplitude showed significant negative correlations with working memory capacity under two and four memory loads ($r = -0.369$, -0.316, adjusted $P < 0.05$). In *BDNF* Val homozygotes, significant negative associations were observed between MMN amplitude and working memory capacity under both two and four memory loads ($r = -0.696$, -0.662, adjusted $P < 0.05$); yet these relationships were not observed in *BDNF* Met-carriers (Fig. 2C–F). The correlations were significantly different in the two *BDNF* genotype groups (two memory loads, $Z = 1.843$, $P = 0.033$; four memory loads, $Z = 1.840$, $P = 0.033$). However, in the multiple linear regression analysis, there was no significant interaction between MMN amplitude and the *BDNF* genotype in relation to working memory capacity under either two or four memory loads, when controlling for covariates including gender, age, PANSS total score, and chlorpromazine equivalents. MMN

Table 1. Differences between *BDNF* Met-carriers and Val homozygotes at baseline.

	Met-carriers $N = 37$		Val homozygotes $N = 17$				
	Mean	SD	Mean	SD	Statistic	*df*	*P*
Age	34.19	7.52	32.06	7.54	$t = 0.967$	52	0.338
Education	14.50	4.04	14.88	2.89	$t = -0.35$	52	0.728
Female/male	22/15		9/8		$\chi^2 = 0.202$	1	0.653
Han nationality/non	33/4		16/1		NA	NA	1.000
Employment/non	15/22		8/9		$\chi^2 = 0.202$	1	0.653
Marriage/non	16/21		5/12		$\chi^2 = 0.938$	1	0.333
Current smoker/non	3/34		3/14		NA	NA	0.365
Clozapine user/non	8/29		1/16		$\chi^2 = 1.099$	1	0.295
Chlorpromazine equivalents	441.18	314.11	443.88	213.70	$t = -0.032$	52	0.974
Duration of illness	12.14	8.51	9.48	7.09	$t = 1.124$	52	0.266
PANSS positive	9.73	3.84	7.65	1.54	$t = 2.839$	51	0.006
PANSS negative	12.86	4.60	11.47	3.56	$t = 1.105$	52	0.274
PANSS general	22.11	4.86	18.76	2.51	$t = 3.325$	51	0.002
PANSS total	44.70	9.14	37.88	6.19	$t = 2.789$	52	0.007
K_T2 (N: 34/17)	1.36	0.47	1.52	0.34	$t = -1.235$	49	0.223
K_T4 (N: 34/17)	1.59	0.80	2.11	0.59	$t = -2.356$	49	0.023
Filtering efficiency_T2 (N: 34/17)	0.27	0.28	0.26	0.29	$t = 0.174$	49	0.863
Filtering efficiency_T4 (N: 34/17)	0.70	0.43	0.84	0.44	$t = -1.014$	49	0.315
MMN amplitude (N: 36/17)	−2.83	1.64	−3.02	1.65	$t = 0.377$	51	0.708

BDNF, brain-derived neurotrophic factor, *PANSS* positive and negative syndrome scale, *K_T2* Cowan's K under only two targets condition of the change detection task, *K_T4* Cowan's K under only four targets condition of the change detection task, *Filtering efficiency_T2* filtering efficiency for two targets, *Filtering efficiency_T4* filtering efficiency for four targets, MMN mismatch negativity.

amplitude did not correlate with interference control in the total sample, *BDNF* Val homozygotes, or *BDNF* Met-carriers (Table 2). The above MMN results obtained from both the two multi-site average clusters and single-site recordings exhibited consistency.

MMN amplitude improvement, *BDNF* genotype, and working memory improvement

All genotype subgroups in the three intervention groups showed balanced baseline characteristics except for the PANSS general symptom ($F_{5,19} = 3.726$, $P = 0.016$) (Supplemental Table 1). In the parietal stimulation group, *BDNF* Val homozygotes exhibited significantly greater improvements in working memory capacity under four memory loads at week 2 compared to Met-carriers ($F_{1,\ 8} = 6.091$, $P = 0.040$) (Fig. 2H). In contrast, in the prefrontal stimulation group, *BDNF* Val homozygotes showed significantly lesser enhancements in working memory capacity under four memory loads at both week 1 and week 2 compared to Met-carriers (all $P < 0.05$) (Fig. 2G). In the sham stimulation group, *BDNF* Val homozygotes had significantly lesser augmentations in working memory capacity under both two and four memory loads at week 1 and week 2 compared to Met-carriers (all $P < 0.05$) (Table 3) (Fig. 2I).

DISCUSSION

This study represents the first exploration into the complex interaction between the *BDNF* genotype and MMN amplitude in relation to working memory in schizophrenia. The findings indicated that *BDNF* Val homozygotes exhibited fewer positive, general symptoms and larger working memory capacity compared to Met-carriers at baseline. A correlation existed between MMN amplitude and working memory capacity within *BDNF* Val homozygotes. The correlations between MMN amplitude and working memory capacity were different in the two *BDNF* genotype groups. However, the multiple linear regression model did not reveal a significant interaction between the *BDNF* genotype and MMN amplitude. This lack of significance might be attributed to the limited sample size, potentially reducing the power to test for multivariate relationships. The longitudinal data further underscored that only in the intervention group with notable MMN amplitude enhancement did *BDNF* Val homozygotes outperform Met-carriers in terms of improvement in working memory capacity.

BDNF Val homozygotes presented with fewer positive and general symptoms compared to Met-carriers, aligning with previous literature[37–39]. Given that patients in this study were clinically stable, the findings were less affected by symptom or medication fluctuations, thus reinforcing the effect of *BDNF* Val/Met polymorphism in schizophrenia symptomatology variation[28]. This study also found that *BDNF* Val homozygotes had greater working memory capacity than Met-carriers. However, the two groups showed no difference in interference control or MMN amplitude. Similarly, ref. [40]. reported that schizophrenia patients with *BDNF* Val/Val performed better during an N-back task. Nevertheless, disparate findings by refs. [41,42]. suggested no connection between the *BDNF* Val/Met polymorphism and working memory in schizophrenia, using the digit span test and letter-number sequencing test. The differences in findings may be attributed to inconsistencies in assessment tools. Moreover, this study indicated that the effect of the *BDNF* genotype on working memory in schizophrenia may be domain-specific and limited to the capacity aspect.

In the total sample, MMN amplitude was negatively correlated with working memory capacity. Similarly, most studies in a systematic review[19] consistently reported a correlation between MMN amplitude and working memory in schizophrenia. Although the current study substantiated a connection between MMN

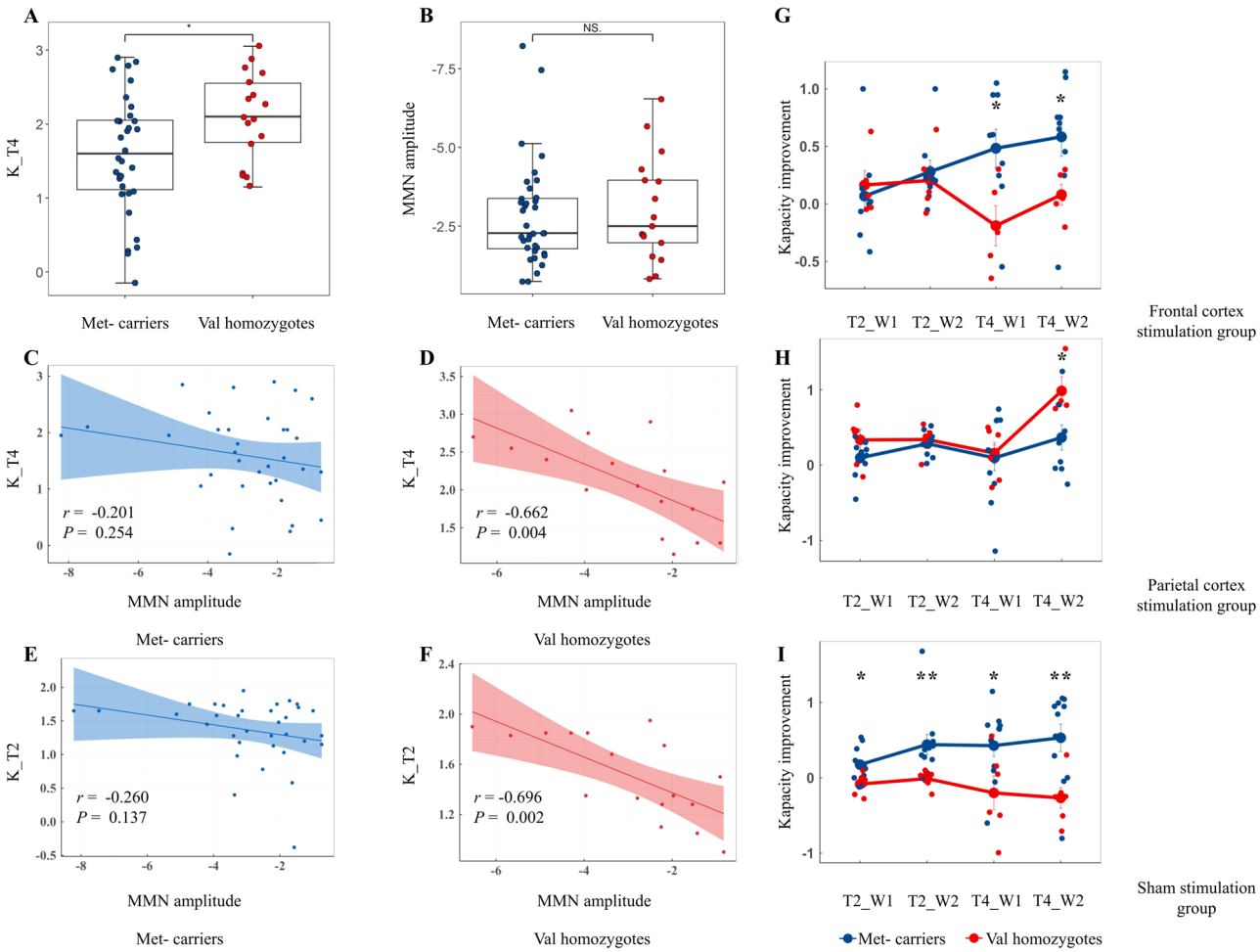

Fig. 2 MMN amplitude, BDNF genotypes and working memory. Comparison of working memory capacity (**A**) and MMN amplitude (**B**) between the two genotype groups. **C**–**F** Correlations between working memory capacity and MMN amplitude across the genotype groups. Effects of *BDNF* genotypes on working memory capacity improvement in the prefrontal stimulation group (**G**), the parietal stimulation group (**H**) and the sham stimulation group (**I**). MMN, mismatch negativity; *BDNF*, brain-derived neurotrophic factor; K_T4, Cowan's K under only four targets condition of the change detection task; K_T2, Cowan's K under only two targets condition of the change detection task; T2_W1, only two targets condition of the change detection task at week 1; T2_W2, only two targets condition of the change detection task at week 2; T4_W1, only four targets condition of the change detection task at week 1; T4_W2, only four targets condition of the change detection task at week 2. *$P < 0.05$, ** $P < 0.01$, NS., not significant.

Table 2. Correlations between working memory and MMN amplitude in *BDNF* Met-carriers, Val homozygotes and total participants at baseline.

		Met-carriers $N = 34$ MMN amplitude	Val homozygotes $N = 17$ MMN amplitude	Total participants $N = 51$ MMN amplitude
K_T2	*r*	−0.260	−0.696	−0.369
	P	0.137	0.002	0.008
K_T4	*r*	−0.201	−0.662	−0.316
	P	0.254	0.004	0.024
Filtering efficiency_T2	*r*	−0.014	−0.115	−0.047
	P	0.936	0.660	0.745
Filtering efficiency_T4	*r*	−0.128	0.016	−0.086
	P	0.469	0.950	0.549

MMN mismatch negativity, *BDNF* brain-derived neurotrophic factor, *K_T2* Cowan's K under only two targets condition of the change detection task, *K_T4* Cowan's K under only four targets condition of the change detection task, *Filtering efficiency_T2* filtering efficiency for two targets, *Filtering efficiency_T4* filtering efficiency for four targets.

amplitude and capacity subdomain, it could not identify a correlation between MMN amplitude and interference control subdomain. This discrepancy could be attributed to working memory capacity being intertwined with theta oscillations, whereas interference control is closely linked to alpha oscillations[43,44]. Notably, MMN primarily reflects theta band activity[45,46].

The correlation between MMN amplitude and working memory was particularly observed in *BDNF* Val homozygotes, suggesting that the Val/Val genotype bolsters the relationship between the NMDAR function and working memory. This may be due to the association of *BDNF* Val/Val genotype with elevated NMDAR-dependent long-term potentiation and depression[29], which are foundational for memory[33]. This study provides clinical evidence for the *BDNF* Val/Met polymorphism modulating NMDAR-mediated synaptic plasticity in schizophrenia. In addition, the findings suggest that *BDNF* Val homozygotes more readily experience NMDAR-mediated improvements in working memory. In line with this inference, some studies have reported greater cortical responses in *BDNF* Val homozygotes than in Met-carriers after neural modulations in a healthy population[47,48]. Su et al[49]. also found that schizophrenia patients with *BDNF* Val homozygotes exhibited enhanced immediate memory after repetitive

Table 3. *BDNF* genotypes and working memory improvement across the three intervention groups.

Group	Working memory improvement	Met-carriers			Val homozygotes			*F*	*df*	*P*
		N	Mean	SD	*N*	Mean	SD			
Frontal cortex stimulation group	K_T2 at week 1	9	0.07	0.40	5	0.17	0.28	0.291	1, 11	0.600
	K_T2 at week 2	9	0.28	0.30	5	0.21	0.28	0.219	1, 9	0.651
	K_T4 at week 1	9	0.48	0.50	5	−0.19	0.39	7.735	1, 10	0.019
	K_T4 at week 2	9	0.58	0.51	5	0.08	0.20	6.853	1, 11	0.023
Parietal cortex stimulation group	K_T2 at week 1	11	0.10	0.23	6	0.33	0.35	2.282	1, 7	0.172
	K_T2 at week 2	9	0.28	0.17	4	0.34	0.24	0.171	1, 4	0.698
	K_T4 at week 1	11	0.10	0.57	6	0.16	0.35	0.079	1, 15	0.782
	K_T4 at week 2	9	0.37	0.50	4	0.99	0.38	6.091	1, 8	0.040
Sham stimulation group	K_T2 at week 1	11	0.17	0.22	6	−0.08	0.14	8.371	1, 14	0.012
	K_T2 at week 2	11	0.44	0.44	6	−0.01	0.12	10.082	1, 12	0.008
	K_T4 at week 1	11	0.43	0.48	6	−0.20	0.55	5.415	1, 9	0.044
	K_T4 at week 2	11	0.53	0.60	6	−0.27	0.34	12.218	1, 15	0.003

BDNF brain-derived neurotrophic factor, *K_T2* Cowan's K under only two targets condition of the change detection task, *K_T4* Cowan's K under only four targets condition of the change detection task, *Filtering efficiency_T2* filtering efficiency for two targets, *Filtering efficiency_T4* filtering efficiency for four targets.

transcranial magnetic stimulation, a response not observed in Met-carriers.

Participants with *BDNF* Val/Val genotype showed superior enhancements in working memory capacity compared to Met-carriers, but only when MMN amplitude was improved. This further substantiates the interactive influence of MMN amplitude and the *BDNF* genotype in relation to working memory capacity in schizophrenia. This phenomenon may be attributed to the increase in glutamatergic activity caused by the improved NMDAR function, offering a broader range of synaptic plasticity and an elevation in BDNF release[50]. This improved the visibility of the effects of the *BDNF* genotype on NMDAR-dependent synaptic plasticity. The findings of other groups in this study can be interpreted as a decrease in the homeostatic level of the excitatory–inhibitory balance when the NMDAR function is not improved, leading to a deterioration of the self-regulation ability to cope with large-scale network activities[51] and impaired or even disrupted activity-dependent regulatory role of BDNF. These results highlight the significance of the interaction between the enhanced NMDAR function and the *BDNF* Val/Met polymorphism for working memory improvements in schizophrenia.

This study, which utilized a modified change detection task, is the first to report an association between MMN amplitude and working memory capacity in schizophrenia. Furthermore, our research provides data from both baseline and post-intervention assessments in a clinical trial, indicating an interaction between *BDNF* genotype and MMN amplitude in relation to working memory capacity in schizophrenia. All participants in this study were in a clinically stable phase, reducing potential confounding impacts on the findings. However, this study also has some limitations. First, the sample size in this study was relatively small, necessitating further validation using larger sample studies. Second, this study lacked a healthy control group. Therefore, it remains unknown whether similar results occur in healthy populations, making it a challenge to discern whether the findings are specific to the state of schizophrenia.

CONCLUSION

In summary, this research revealed a noteworthy interaction between MMN and *BDNF* Val/Met polymorphism in relation to working memory capacity. The results contribute to our current understanding of the pathological mechanisms underlying the deficits in working memory capacity. Additionally, they provide valuable guidance for future intervention studies, particularly those mediated by NMDAR, aimed at addressing working memory deficits in schizophrenia.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author (C.Y.W).

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AUTHOR CONTRIBUTIONS

The project was designed by W.H., X.C., X..L., F.Z., and C.W. Data collection was carried out by H.L., Q.W., Y.D., and R.W. Data analysis was performed by W.H., X.Q., and F.D. The manuscript was written and revised by W.H., Q.B., X.L., F.Z., and C.W.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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