Theta Oscillation and Functional Connectivity Alterations Related to Cerebral Small Vessel Disease with Working Memory Impairment

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Research Article

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Abstract

Background

Impaired working memory (WM) is an important clinical symptom of cognitive dysfunction associated with cerebral small vessel disease (CSVD). Theta oscillations play an important role in the regulation of learning, WM and synaptic plasticity. Therefore, we speculate that theta oscillation may play an important role in the process of working memory impairment in CSVD.

Methods

Seventy-eight patients with CSVD (mean age 66.18 ± 1.42) and 49 healthy controls (HCs) (mean age 66.53 ± 1.3) were recruited to perform the WM task. Neural oscillations and functional connectivity during the encoding, maintenance, and retrieval phases of WM were evaluated during performance of WM test.

Results

Compared with the control group, the working memory behavior of the CSVD group showed a significantly longer reaction time and lower accuracy rate. The energy density and functional connection (FC) strength of the theta band in frontal region of the CSVD group were significantly lower than those of the control group, and the theta oscillation in the retrieval phase was significantly higher than that in the coding phase. However, there was no significant change in FC strengths among three phases. Both in the two groups, the FC was significantly positively correlated with accuracy and negatively correlated with reaction time (RT).

Conclusion

Our results indicated that CSVD patients have significant working memory impairment, and the lack of theta oscillation in the frontal region and the abnormal functional connection of the brain network may be one of its potential neurophysiological mechanisms.

Background

Cerebral small vessel disease (CSVD) refers to a pathological process that affects cerebral arterioles, venules and capillaries, resulting in damage to deep gray and white matter tissues [1]. In CSVD, white matter damage will reduce the efficiency of gray matter connections and destroy the neural network that supports cognitive ability [2, 3]. What is particularly affected in CSVD is executive function abilities, including mental flexibility and the ability to monitor performance. There are also obstacles to working memory, and the mnemonic function related to working memory relies on the network in the brain that has a strong connection with the frontal lobe [4, 5]. Working memory combines executive and memory

functions, and related cognitive operations require information maintenance, synchronization, and update [6].

Damage in CSVD is focused on the white matter [1], the location of this damage may damage the direct communication pathways between different brain regions, thereby limiting information transmission [7]. The performance of working memory requires repeated integration of information across multiple brain regions. Brain damage in CSVD greatly hinders the execution of working memory [1, 8, 9]. Working memory is mainly supported by the frontal and parietal cortex networks during development [10]. The frontal-parietal network is the foundation of WM, in which the prefrontal cortex (PFC) plays a key role. Multi-channel electroencephalographs (EEGs) studies have found that theta oscillations are mainly generated in the PFC and persist in the WM lag phase, which plays an important role in the maintenance of information [11]. Working memory is a system with limited capacity for temporary storage and processing of information in cognitive tasks. It is the basis of high-level cognitive activities such as reasoning, judgment, and thinking which is an important concept for evaluating cognitive functions [12]. Therefore, the research on the mechanism of CSVD working memory impairment, may be of great significance to the diagnosis and treatment of CSVD, formulating targeted treatment strategies and evaluating prognosis.

According to the physiological significance of EEG, δ oscillation is 0–4 Hz, θ oscillation is 4–8 Hz, α oscillation is 8–13 Hz, β oscillation is 13–30 Hz, γ oscillation is 30–100 Hz. A wide range of of studies have found that different frequency bands of neural oscillations are closely related to cognitive behavior [13]. Theta oscillation plays an important role in cognitive behavior (including working memory), and the energy enhancement of theta activity is closely related to the successful execution of working memory tasks [13]. Studies have found that theta oscillations participate in the edge-prefrontal cortex interaction through network synchronization activities [14]. Previous studies have shown that theta oscillations are associated with higher cognitive control needs and increase power during the execution of WM tasks [11, 15].

Therefore, this study records the behavior and EEGs of patients with CSVD during the execution of WM tasks, from the perspective of EEG theta oscillations, based on analyzing the energy density distribution of EEGs in theta frequency, constructs a functionally connected brain network. To explore the potential brain network mechanism of working memory impairment in patients with CSVD. This basic and innovative research idea has enlightening significance for the neurophysiological mechanism of other nervous system-related cognitive disorders, and provides a new evaluation method for the early detection, diagnosis and treatment of CSVD-related cognitive disorders in clinical practice.

Methods

Participants

Seventy-eight patients with CSVD and 49 HCs were recruited from the second hospital of Tianjin Medical University, Tianjin, China. In order to exclude the influence of cognitive impairment on CSVD patients, only screened CSVD patients without cognitive impairment as participants. The inclusion criteria: 1. White matter hyperintensities were graded by using the Fazekas scale (0 to 3); 2. The Staals classification was used to determine presence of CSVD (defined as a Staals classification of >1, which consists of 1 or more of the following findings: white matter hyperintensities with Fazekas score >1; ≥1 microbleed; ≥1 lacunar infarct; and moderately to severely enlarged perivascular spaces in the basal ganglia) [16]. The exclusion criteria: 1. cognitive impairment: Montreal Cognitive Assessment (MoCA) scores ‹ 26 and mini mental state examination (MMSE) scores ‹ 27; 2. use of psychotropic drugs; 3.Serious physical and mental diseases (such as epilepsy, encephalitis, hydrocephalus, hypothyroidism, alcoholism, drugs or anxiety, depression and other physical and mental diseases, etc.). Healthy volunteers whose age, gender, and educational background matched the CSVD group were recruited as the control group. They were all right-handed and had no neurological and mental diseases that affect cognitive function. This study was approved by the ethics committee of the second hospital of Tianjin Medical University, and written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Eeg Acquisition And Preprocessing

Use Nicolet EEG (YZB/USA 2783-2011) with 25 electrodes to record neural signals (FP1, FP2, AF3, AF4, F7, F3, Fz, F4, F8, FC3, FC4, T3, C3, Cz, C4, T4, CP3, CP4, T5, P3, Pz, P4, T6, O1 and O2) according to the extend 10–20 system while the participants performed WM tasks. The reason for choosing 25 electrodes is that previous studies have shown that working memory mainly involves the frontal and parietal regions [4, 5, 10, 11, 17]. Therefore, in order to further study the function of the two brain regions, an additional 6 electrodes (AF3, AF4, FC3, FC4, CP3, CP4) are added to the frontal and parietal regions on the basis of the standard 19 electrodes. All channels are below 5 kΩ. The signal undergoes offline low-pass filtering (100 Hz), 1,024 Hz sampling, and notch filtering (49–51 Hz). The signals were recorded and analyzed using MATLAB (2012a) and baseline drifts were removed by curve fitting method. The acquired signal refers to the average value of all channels [18].

Behavioral Paradigm

We adopted the delay matching sample (DMS) paradigm and the schematic is shown in Figure 1A. Subjects were tested in a quiet environment, and formal experiments were started after practicing and familiarizing with the operating procedures. First, the red "*" of the visual pattern is displayed on the screen. After a short delay (gaze time is 0.5 s), four patterns appear sequentially (each pattern lasts for 1 s, the connection time of the front and back two patterns is 0.013 s). After the four patterns appear, the screen displays red "+". At this time, it is required to recall the first four patterns (delay period is 3 s). At the end of the delay period, another judgment pattern appears, which requires as accurate as possible. And as soon as possible to determine whether the pattern has appeared in the previous 4 patterns, if it has

appeared (i.e. matched), select "1", if it has not appeared (i.e. mismatched), select "2", all keys are operated by the right hand. After the key is selected, the pattern disappears, the screen is blank for 4s, and enters the next test. If the reaction time is too long (more than 2.5s), the pattern disappears automatically and enters the next test. Each experimental link includes 10 tests, each with at least 5 cycles. The patterns used in the experiment were extracted from the Snodgrass picture library. Behavioral data were recorded by E-prime2.0 software.

Functional Connection Calculations

A method of analyzing the interaction between multiple variables has been widely used in the field of computational neuroscience, namely Granger causality analysis.

The functional connection (FC) is obtained through the multivariate autoregressive model (MVAR). The directional transfer function (DTF) is an indicator used to express the FC. It is a refinement method based on MVAR and is considered to be useful method of causality analysis in the field of computational neuroscience [19]. In the framework of the MVAR model, the DTF was formulated. Define the DTF from channel *j* to channel *i*, which represents the causal effect from channel *j* to channel *i* at frequency f, and the calculation formula is as follows:

$$\gamma_{ij}(f)^2 = \left|H_{ij}\right|^2 / \sum_{m=1}^{N} \left|H_{im}\right|^2$$

where γ_{ij} (f) represents the ratio of the inflow from channel *j* to channel *i* to all the other inflows to channel *i*, *H* is the transfer matrices and *k* is the number of the channels. The mean DTF value is a direct measurement of FC strengths among EEGs.

DTF matrix corresponding to 25 electrodes, and it is an index directly describing the causal connection strength of working memory EEGs. The calculation formula is as follows:

$$DTF_{global} = \frac{\sum_{i \in K} \sum_{j \neq i \in K} \gamma_{ij}}{k(k-1)}$$

k is the number of all channels and *K* is the set of all channels.

DTF_i is a major indicator of channel *i* activity in causal networks. The causal network is constructed on the basis of DTF matrix, in which the DTF_i calculation formula is as follows:

$$DTF_i = \frac{1}{2(k-1)} \sum_{j \neq i \in V} (\gamma_{ji} + \gamma_{ij})$$

k represents the number of channels and *V* represents the set of channels in the causal network.

The causal network of the whole brain was constructed according to the causal connection strength of 25 channels.

Statistical analysis

In this study, statistical analysis was performed by using SPSS version 20.0 (SPSS Inc., Chicago, Illinois). Independent sample t-test was used to analyze the baseline data, WM behavior (behavioral accuracy and RT), functional connectivity strengths and power density between the two groups. Data in the text and figures are expressed as means ± SEM. Intra-group comparisons among different frequency bands (delta, theta, alpha, beta and gamma), different WM phases (encoding, maintenance, and retrieval), and different brain regions (frontal, parietal, occipital, and temporal) were all statistically analyzed by analysis of variance (ANOVA). Multiple comparisons between groups were compared with least significant difference (LSD). Pearson correlation was used to analyze the correlation between WM behavior indicators of WM (RT and accuracy) and FC strength during the WM tasks. Tests with a P value less than or equal to 0.05 were considered statistically significant (***P < 0.001, **P < 0.01 and *P < 0.05).

Result

Demographic and clinical data

Table 1 summarized the basic demographic and clinical characteristics. There were no statistically significant differences in age and gender between-group. The mean MMSE score of HCs was 28.59 ± 1.01 and the range was 27–30, the score of CSVD was 28.30 ±0.89 and the range was 27–30. The mean MoCA score of HCs was 27.62 ± 1.27 and the range was 26–30, the score of CSVD was 27.38 ± 1.05 and the range was 26–30. There were no significant differences in MMSE and MoCA scores between the two groups.

Table 1 Baseline data of subjects				
Basic information	CSVD (n=78)	HC (n=49)	t/x^2	*P*
Demographics				
Age (year, $\bar{x} \pm s$)	66.18 ± 1.42	66.53 ± 1.30	1.396	0.165
Male (n, %)	48, 61.54%	29, 59.18%	0.070	0.791
Education (year, $\bar{x} \pm s$)	9.47 ± 1.94	9.88 ± 2.00	1.146	0.254
Cognitive function scale (score, $\bar{x} \pm s$)				
MMSE	28.30 ± 0.89	28.59 ± 1.01	1.696	0.092
MoCA	27.38 ± 1.05	27.62 ± 1.27	1.155	0.250

Behavioral performance

WM task accuracy and RT were analyzed between the two groups. The correct rate was significantly lower than the HC group(68.26±1.81 vs 83.5±3.39), shown in Figure 1B. Response time in CSVD group was significantly longer than that in HC group（1756.48±42.8ms vs 1262.48±41.79ms）, shown in Figure 1C, The difference was statistically significant（all P<0.01）, which suggested that WM behavior disorder existed in CSVD group.

Time-frequency analysis

Apply the short-time Fourier transform to obtain the time-frequency distribution of the EEGs of the characteristic channel during the WM task. During the correct trials, the time-frequency distribution of Fz in the HC group is shown in Fig. 2A. The diagram shows that the energy density of theta band is most obvious when executing tasks. During the correct trials, the time-frequency distribution of Fz in the CSVD group is shown in Fig. 2B. The diagram shows that the energy density of theta band is most obvious when executing tasks. Compared the power of different bands: in Fig. 2C, the power of theta band was higher than other bands in the HC group (theta/delta: t = 5.188, P < 0.001; theta/alpha: t = 5.522, P < 0.001; theta/beta: t = 48.37, P < 0.001; theta/gamma: t=53.06, P< 0.001), in Fig. 2D, the power of theta band was higher than other bands in the CSVD group (theta/delta: t = 4.782, P < 0.001; theta/alpha: t = 5.758, P < 0.001; theta/beta: t = 55.15, P < 0.001; theta/gamma: t=41.42, P< 0.001). Then, we compared the power of the five bands between the two groups (Fig. 2E). Compared with the HC group, the CSVD group exhibited significantly decreased theta band (t = 13.43, P < 0.001), beta band (t = 14.60, P < 0.001), gamma band (t = 3.763, P < 0.001) and alpha band (t = 2.691, P < 0.05). The delta band was no statistical difference (t = 1.65, P = 0.0.122) between the two groups. Fig. 2F shows the variation curve of whole brain average power density with frequency during the WM tasks for the HC group. Fig. 2G shows the variation curve of whole brain average power density with frequency during the WM tasks for the CSVD group. Fig. 2H shows the comparation curve of whole brain average power density with frequency during the WM tasks between the two groups. In Fig. 2I, we compared the 25 channel average power in theta band at each phase of WM task in the HC group, the power of encoding phase was lower than other phase (encoding/maintenance: t = 3.068, P < 0.01; encoding/retrieval: t = 4.009, P < 0.001). The power was no statistical difference between the maintenance phase and the retrieval phase in the HC group (t = 1.539, P = 0.125). In Fig. 2J, we compared the 25 channel average power in theta band at each phase of WM task in the CSVD group, the power of retrieval phase was higher than other phase (encoding/retrieval: t = 8.321, P < 0.01; maintenance/retrieval: t = 7.431, P < 0.001). The power was no statistical difference between the encoding phase and the maintenance phase in the CSVD group (t = 1.018, P = 0.309). Then, we compared the 25 channel average power in theta band at each phase between the two groups (Fig. 2K). The CSVD group exhibited significantly decreased encoding phase (t = 26.09, P < 0.001), maintenance phase (t = 24.52, P < 0.001) and retrieval phase (t = 26.73, P < 0.05) compared to that of the HC group.

Figure 3A, D, G show the energy topography of the theta band among the three phases in the HC group. Fig. 3B, E, H show the energy topography of the theta band among the three phases in the CSVD group. Both in the two groups, the topographic map shows the theta activity related to the frontal region, especially in the Fz channel in the midline area of the frontal region. We compared the power of the four brain regions between the two groups. In Fig. 3C, compared with the HC group, significantly decreased theta power during the encoding phase of the CSVD group in frontal region ($t = 6.749$, $P < 0.001$), parietal region ($t = 3.923$, $P < 0.01$), temporal region ($t = 11.29$, $P < 0.001$) and occipital region ($t = 11.21$, $P < 0.01$). From Fig. 3F, Compared with the HC group, significantly decreased theta power during the maintenance phase of the CSVD group in frontal region ($t = 6.766$, $P < 0.001$), parietal region ($t = 3.067$, $P < 0.01$) and temporal region ($t = 12.23$, $P < 0.001$). There was no statistical difference in occipital region ($t = 3.557$, $P = 0.071$). From Fig. 3I, Compared with the HC group, significantly decreased theta power during the retrieval phase of the CSVD group in frontal region ($t = 6.78$, $P < 0.001$), parietal region ($t = 2.958$, $P < 0.05$), temporal region ($t = 10.15$, $P < 0.001$) and occipital region ($t = 21.38$, $P < 0.01$) .

Functional connectivity across electrodes during WM tasks

The DTF value was used to evaluate the FC strength (theta band) during the WM task in the HC and CSVD groups. In Fig. 4, showed three phases connection matrix during the WM tasks of the two groups. Both in the two groups, DTF was mainly concentrated in the frontal region, especially in the Fz channel. However, Compaired to the HC group (Figure 4A, D, G), the FC strength of the CSVD group (Fig. 4B, E, H) was significantly weakened (the encoding phase, Fig. 4C, $t = 14.220$, $P < 0.001$; the maintenance phase, Fig. 4F, $t = 7.765$, $P < 0.001$); the retrieval phase, Fig. 4I, $t = 13.030$, $P < 0.001$). In addition, we compared the FC strength in theta band among three phases of WM task, both in the HC group ($F = 0.28$, $df = 2$, $P = 0.752$) and the CSVD group ($F = 0.33$, $df = 2$, $P = 0.718$) were no statistically difference. This indicates that it is the disease group rather than the phase of the WM task that affects the functional connectivity strength.

Functional connectivity distribution during the WM tasks

We use the topographic maps of DTF distribution to evaluate the spatial distribution of FC during the WM tasks. Consistent with the results of the previous study on neural oscillations, both in the two groups, the spatial distribution of DTF was mainly concentrated in the frontal region (Fig. 5A and B). The strength of FC in the CSVD group was significantly lower in the frontal region than the HC group (Figure 5C, $t = 5.965$, $P <0.001$). In addition, we further analyzed the FC of frontal region outflow and frontal region inflow. Figures 6A and B respectively show the average DTF matrices of the two groups in the four brain regions. The FC distribution mainly includes the frontal-frontal, frontal-parietal, and frontal-occipital in the HC groups (Fig. 6A). In the CSVD group (Fig. 6B), there were low strength and disordered connectivity among the four brain regions. From Fig. 6C, the FC strength of frontal outflow and the frontal inflow in the CSVD group were significantly lower than the HC group ($t = 4.579$, $P <0.001$; $t = 5.402$, $P <0.001$).

Correlation analysis

We calculated the Pearson correlation between DTF and behavioral indicators to further clarify the relationship between the strength of FC and behavioral performance in patients with CSVD. As shown in Figure 7A and B, there was a significant positive correlation between DTF and accuracy in both groups (CSVD: $p < 0.001$, $r = 0.966$, HC：$p < 0.001$, $r = 0.773$). There was a significant negative correlation between DTF and reaction time in both groups (CSVD：$p < 0.001$, $r = -0.763$, HC：$p < 0.001$, $r = -0.963$).

Discussion

The results indicated that during the WM tasks, compared with the HC group, the theta oscillation and FC of the frontal region of the CSVD group were significantly weakened, but during the execution of the WM tasks, the dominant functions of the two groups in the frontal lobe were obvious. Therefore, we demonstrated that the frontal region was the principal brain region in the working memory network. Furthermore, FC in the frontal region was not observed statistical difference in the three phases of WM of the CSVD group and HC group, which suggests that it is the disease grouping rather than the period of WM task that affects the strength of functional connection. The functional network in the frontal lobes of CSVD patients has changed, which is characterized by the reduction of the number of connections and the strength of connections, which means the dynamic coordination between nerve activity signals is reduced. These differences in theta oscillation and FC found in the study illustrated that the reduction of theta oscillation and FC in the frontal region may be a potential mechanism for CSVD patients with cognitive impairment.

In this study, we calculated the strength of functional connectivity in each brain region and found the strongest functional connectivity in the frontal midline region, confirming the importance of the frontal lobe in performing working memory tasks, The role of frontal midline theta oscillatory activity is often interpreted as a manifestation of increased cognitive demands required for task completion and is associated with the following functions: mental effort, concentration, cognitive control, and resource allocation [20], but it is also associated with maintaining information in short-term or working memory [21]. Theta band transmit more strongly in frontal to parietal and frontal regions when comparing tests requiring information integration [22] and imaging studies have also reported the involvement of frontal lobe regions in WM tasks [23], These are consistent with the results of our study. Our results also showed that the FC strength of the frontal region was weaker in the CSVD group than in the HC group, which may be the reason why CSVD patients showed insufficient reaction time and correct rate during the performance of working memory tasks. This suggests that the effect of CSVD on cognition may depend on location, which means that location should be considered in order to more accurately identify lesions that contribute to cognitive symptoms in individual patients.

The mechanism underlying the absence of theta oscillations in patients with CSVD leading to WM disorder is not clear. Possible reasons follow: 1. Cerebral ischemia caused by CSVD may directly interrupt the frontal subcortical pathway and long-range fiber connections [24, 25], leading to the absence of theta oscillations in the frontal lobe and the absence of suchoscillations associated with the frontal lobe in the hippocampus, which leads to WM disorder. Small blood vessels disease is mainly manifested as

impairment of frontal lobe subcortical function, while impairment of executive function is most common[26, 27]. Ischemic white matter lesions at any location were associated with decreased glucose metabolism in the frontal cortex and decreased executive function of patients[28]. Other studies have found that the decrease in glucose metabolism in the frontal lobe caused by subcortical small vessel disease is also related to adecrease in intelligence level and impairment of memory function[29]. Furthermore, cerebral ischemia caused by CSVD may cause hippocampal atrophy, which directly or indirectly could lead to the loss of theta oscillation, causing WM disorder[29]. Down regulation of mRNA expression of the hyperpolarization-activated cyclic nucleotide-gated channel (HCN channel) 2 in the hippocampal CA1 region is associated with cognitive dysfunction caused by chronic cerebral ischemia[30]. Meanwhile, spatial WM injury induced by chronic cerebral ischemia was related to down regulation of HCN2 expression in the PFC, while reversing the down regulation of HCN2 expression in the PFC improved spatial WM deficits[31].

Limitations

This experiment is a single-center study, excluding patients with severe cognitive impairment who cannot cooperate, and the results may have selection bias. Secondly, EEG cannot directly study the hippocampus, and animal-based experiments are needed to study the hippocampus through intracranial electrodes. The next step is to continue the multi-center, larger sample size study, subdivide CSVD patients into groups according to the changes of imaging, and do more in-depth analysis in combination with hippocampus, to closely combine neuroimaging with neuroelectrophysiology, to provide new ideas for clinical research on the mechanism of cognitive dysfunction in CSVD.

Conclusions

In conclusion, our results showed that the functional connectivity strength of theta band in the frontal lobe in HC increased during the working memory task, while that in CSVD patients was relatively weak. It is hypothesized that increasing functional connectivity strength in the frontal lobe in theta band is necessary to perform working memory tasks; therefore, reduced functional connectivity strength in the frontal lobe may provide a potential mechanism for working memory deficits in CSVD patients. From the perspective of functional brain network, individualized analysis of EEG signals during the execution of working memory lays a foundation for future research on the mechanism of cognitive dysfunction in CSVD, has a certain guiding role for early clinical detection of patients with working memory impairment, and provides a new idea for brain network analysis of WM in CSVD patients.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of The Second Hospital of Tianjin Medical University. All participants have signed an informed consent form. All processes involving humans are conducted in

accordance with the ethical standards of the research committee of this institution and the 1964 Helsinki Declaration and subsequent amendments or similar ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to the complexity and uniqueness of the raw EEG data, as well as the limitations of laboratory policies but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare no competing interests.

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Authors' contributions

YG and XT conceived and designed the research; YG and QD searched the literature; YG analyzed data and prepared tables and figures; YG and QD drafted the manuscript; XL, XX and XT critically reviewed and revised the manuscript and contributed to the discussion and all authors read and approved the final version of the submitted manuscript.

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Figures

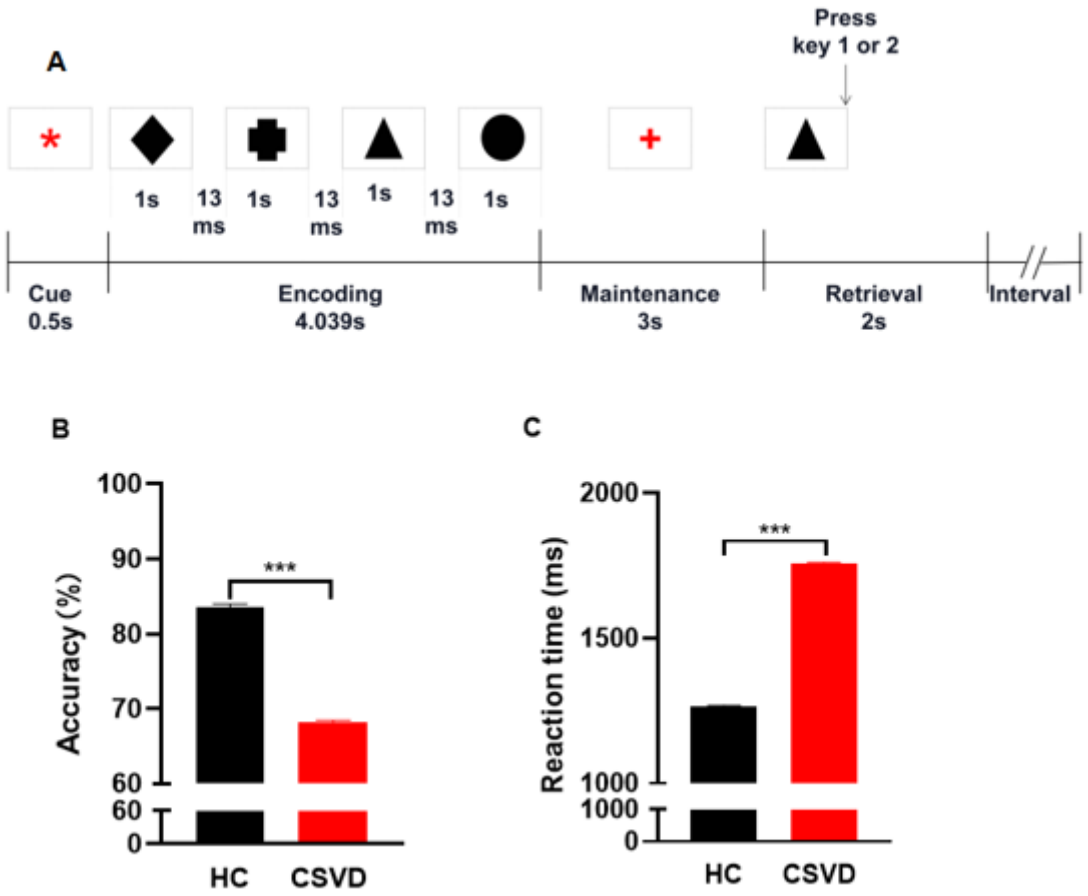

Figure 1

Schematic diagram of electrode partition and behavior.

(A) DMS schematic diagram. (B) Compared with HC group, the reaction time of CSVD group was significantly prolonged(t-test，P<0.001). (C) Compared with HC group, the accuracy of WM task in CSVD group was significantly reduced(t-test，P<0.001). Error line representation SEM. DMS，Delay matching sample，HC，Healthy control，CSVD，Cerebrovascular disease，SEM，Mean standard deviation.

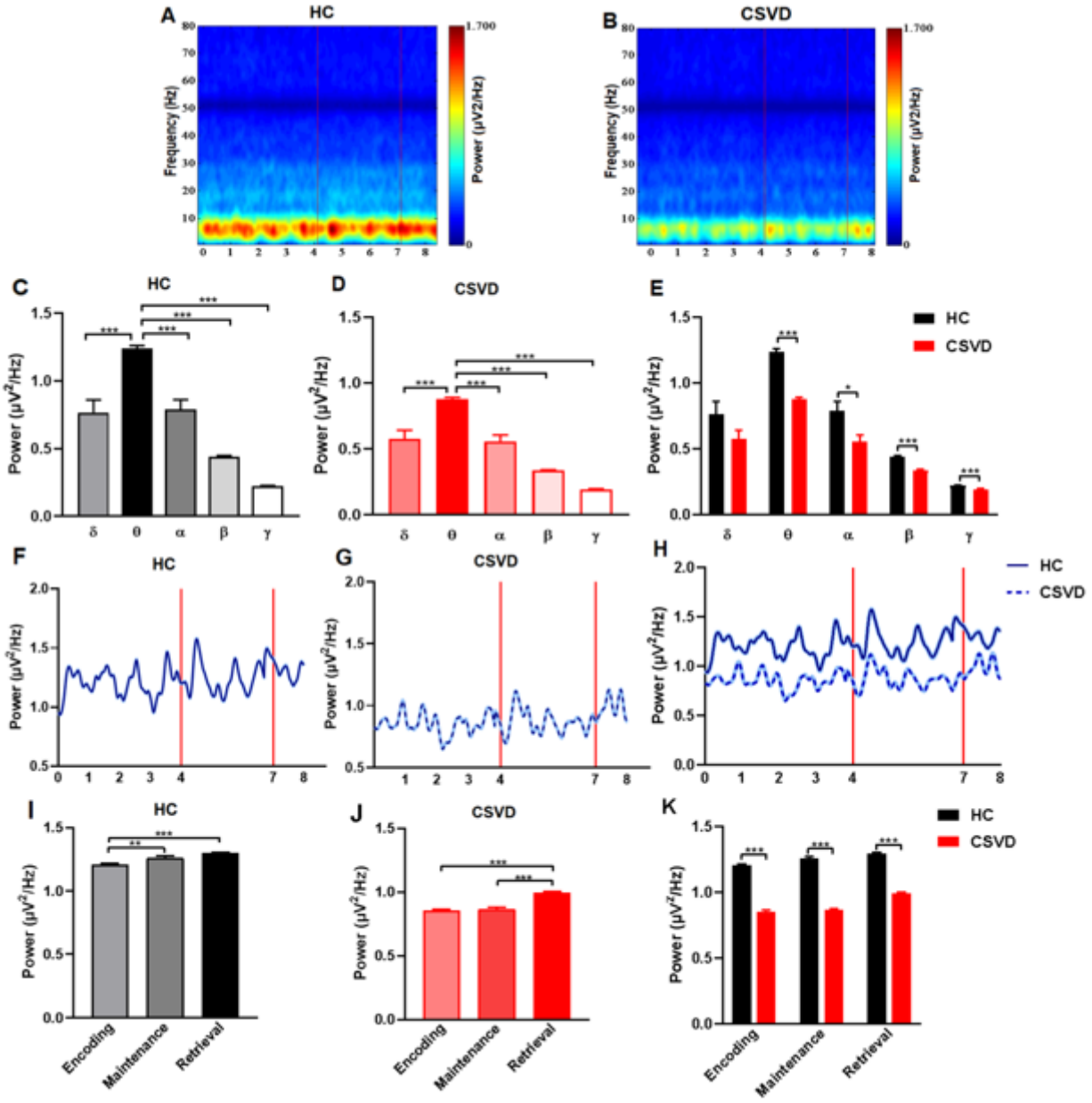

Figure 2

Electroencephalogram spectrograms during WM tasks

Average time–frequency power spectrum of the Fz channel in the HC group. Time is on the x-axis and frequency is on the y-axis. The red vertical line indicates the response point. Power is indicated by color. (B) Average time-frequency power spectrum of the Fz channel in the CSVD group. (C) Averaged power distribution histogram of the HC group. The power of the theta band was significantly greater than that of other frequency bands (LSD, $P < 0.001$). (D) Averaged power distribution histogram of the CSVD group. The power of the theta band was significantly greater than that of other frequency bands (LSD, $P < 0.001$). (E) Comparison of averaged power of the 5 frequency bands between the two groups. The CSVD group exhibited significantly decreased theta, alpha, beta and gamma power compared to that of the HC group (t-test, $P < 0.05$). (F) Average time power curve of the theta band in the HC group. (G) Average time

power curve of the theta band in the CSVD group. (H) Comparison of averaged time power of the theta bands between the two groups. (I) Averaged power distribution histogram of the HC group. The power of the encoding phase was significantly lower than that of other phases (LSD, P < 0.01). (J) Averaged power distribution histogram of the CSVD group. The power of the retrieval phase was significantly greater than that of other phases (LSD, P < 0.01). (K) Comparison of averaged power of the 3 phases between the two groups. The CSVD group exhibited significantly decreased among three phases compared to that of the HC group (t-test, P < 0.001). Error line representation SEM. HC：Healthy control；CSVD：Cerebral small vascular disease；LSD, least significant difference.

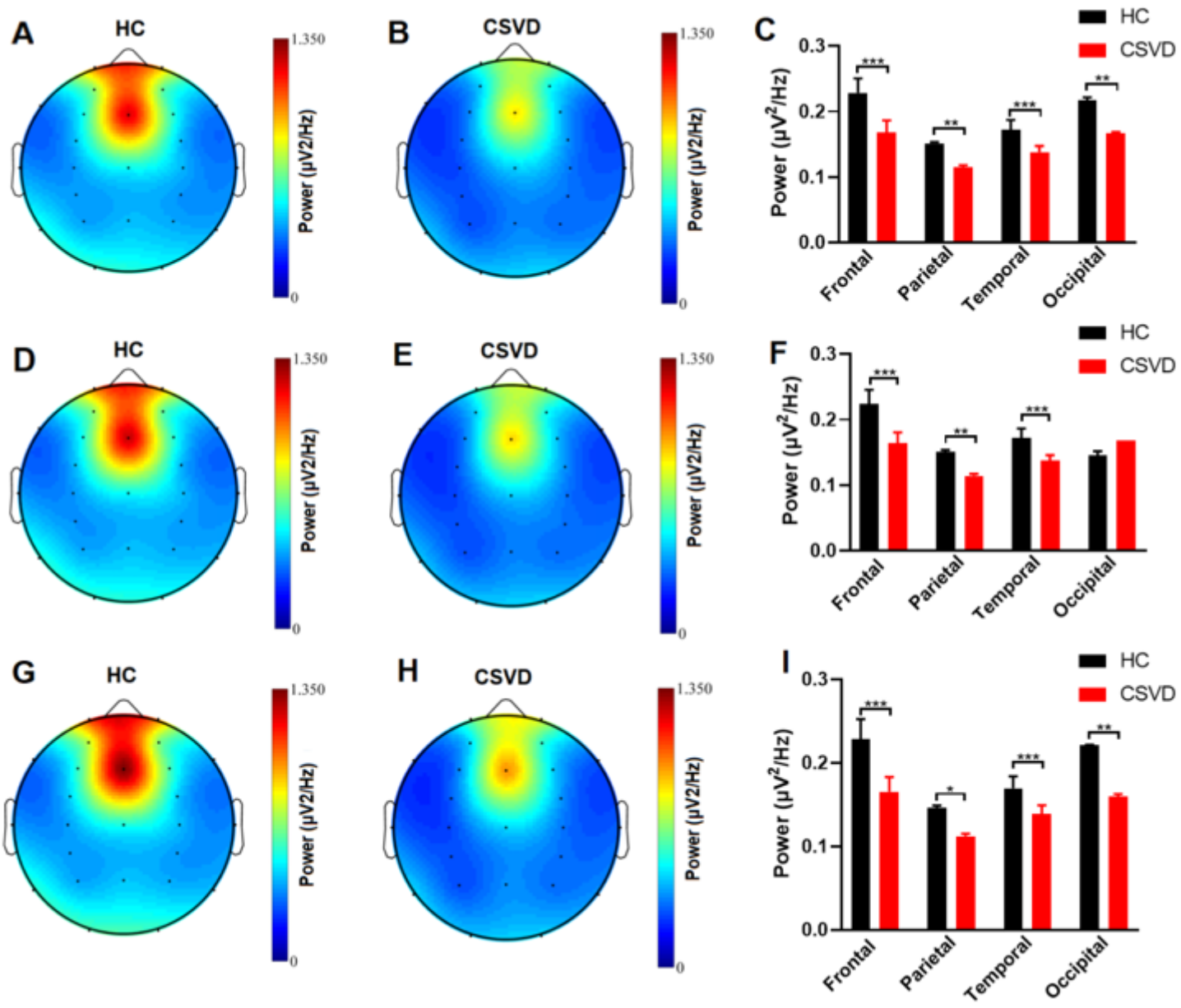

Figure 3

Spatial distribution of power during the WM tasks.

The topographical map of power in encoding phase during WM tasks in the HC group. Power is indicated by color. (B) The topographical map of power in encoding phase during WM tasks in the CSVD group. (C) Comparison of averaged power of encoding phase in the four brain regions between the two groups. The CSVD group exhibited significantly decreased in frontal region, parietal region and occipital region compared to that of the HC group (t-test, P < 0.05). (D) The topographical map of power in maintenance phase during WM tasks in the HC group. (E) The topographical map of power in maintenance phase during WM tasks in the CSVD group. (F) Comparison of averaged power of maintenance phase in the four brain regions between the two groups. The CSVD group exhibited significantly decreased in frontal region and parietal region compared to that of the HC group (t-test, P < 0.05). (G) The topographical map of power in retrieval phase during WM tasks in the HC group. (H) The topographical map of power in retrieval phase during WM tasks in the CSVD group. (I) Comparison of averaged power of retrieval phase in the four brain regions between the two groups. The CSVD group exhibited significantly decreased in frontal region, parietal region and occipital region compared to that of the HC group (t-test, P < 0.05).

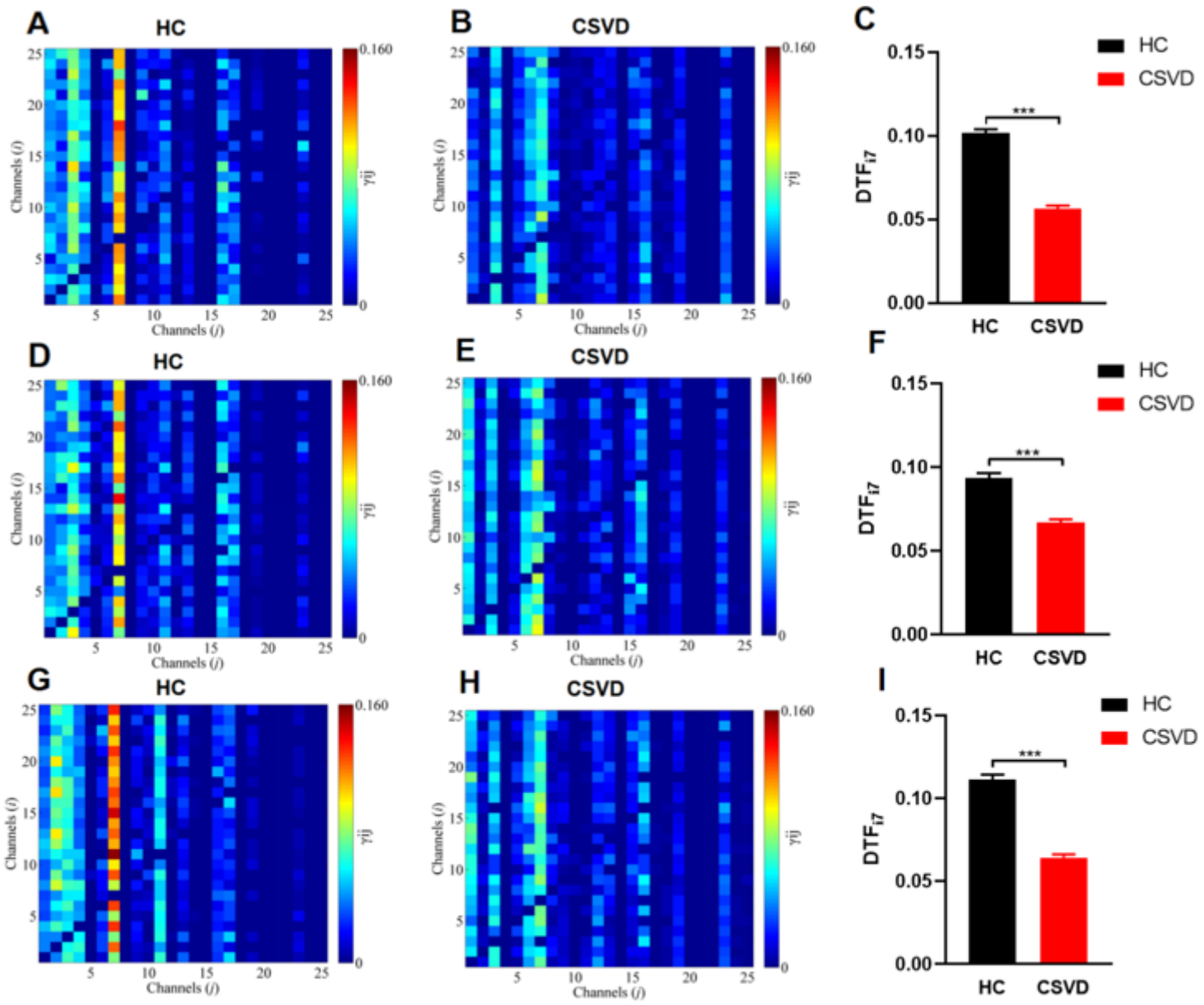

Figure 4

Functional connectivity across electrodes during WM tasks.

(A) Connectivity matrices of encoding phase in the HC group. The extent to which each node interacts with each other node. Each node represents a channel. The scaled colors represent the connectivity strengths from channel j to channel i. (B) Connectivity matrices of encoding phase in the CSVD group. (C) Comparison of average DTF_{i7} between the two groups in encoding phase. Compared with the HC group, the CSVD group exhibited significantly decreased functional connectivity during the WM tasks (t-test, $P < 0.001$). (D) Connectivity matrices of maintenance phase in the HC group. (E) Connectivity matrices of maintenance phase in the CSVD group. (F) Comparison of average DTF_{i7} between the two groups in maintenance phase. Compared with the HC group, the CSVD group exhibited significantly decreased functional connectivity during the WM tasks (t-test, $P < 0.001$). (G) Connectivity matrices of retrieval phase in the HC group. (H) Connectivity matrices of retrieval phase in the CSVD group. (I) Comparison of average DTF_{i7} between the two groups in retrieval phase. Compared with the HC group, the CSVD group exhibited significantly decreased functional connectivity during the WM tasks (t-test, $P < 0.001$).

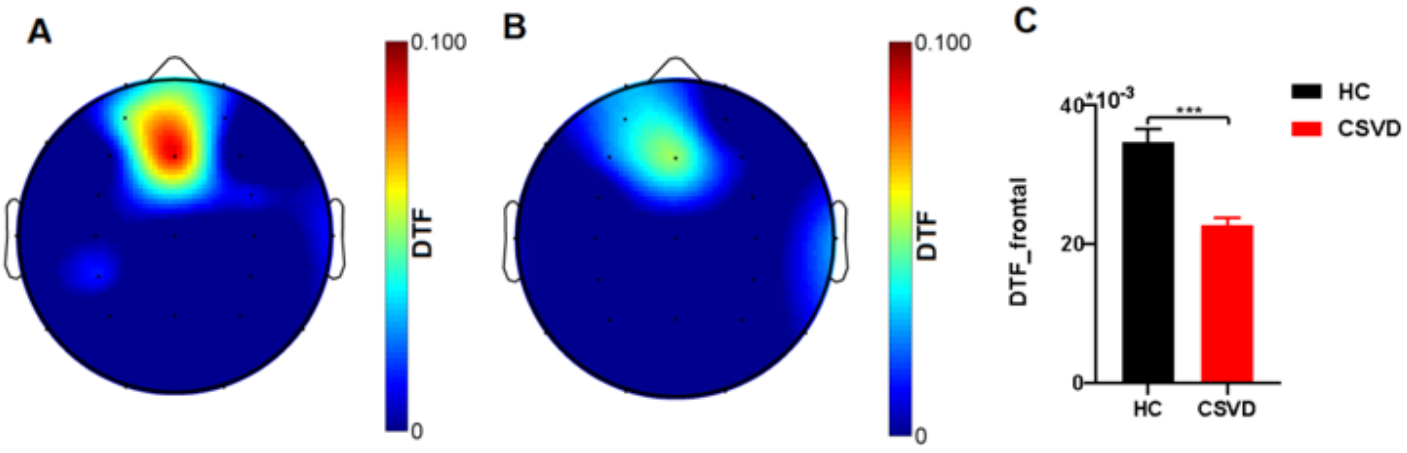

Figure 5

Functional connectivity distribution during the WM tasks.

(A) The topographical map of the DTF in the HC group during the tasks. The scaled colors represent connectivity strengths. (B) The topographical map of the DTF in the CSVD group. (C) Comparison of the average DTF in the frontal region between the two groups. The CSVD group exhibited significantly decreased functional connectivity than the HC groups during the WM tasks (t-test, $P < 0.001$). WM, working memory; DTF, directed transform function; HC, healthy control; CSVD, Cerebral small vascular disease.

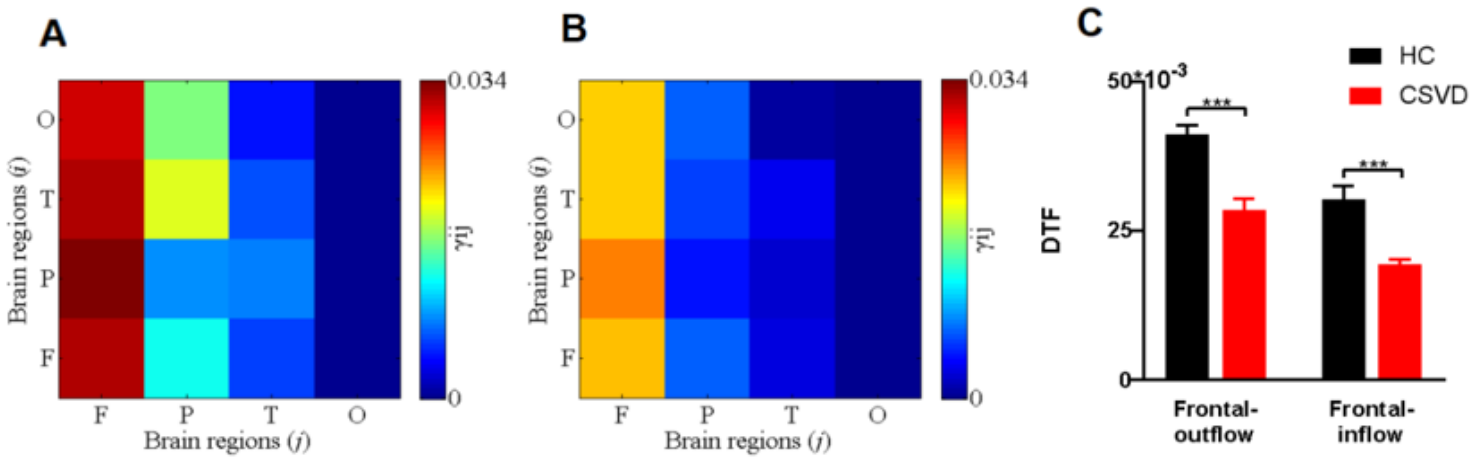

Figure 6

Functional connectivity among brain regions during the WM tasks.

(A) Connectivity matrices of the four brain regions in the HC group. Each node represents a brain region. The scaled colors represent the connectivity strengths from channel j to channel i. (B) Connectivity matrices of the four brain regions in the CSVD group. (C) Comparison of the average DTF in the frontal regions between the two groups. The CSVD group exhibited significantly decreased functional connectivity in frontal outflow and frontal inflow compared with the HC group during the WM tasks (t-test, P < 0.001). WM, working memory; DTF, directed transform function; HC, healthy control; CSVD, Cerebral small vascular disease.

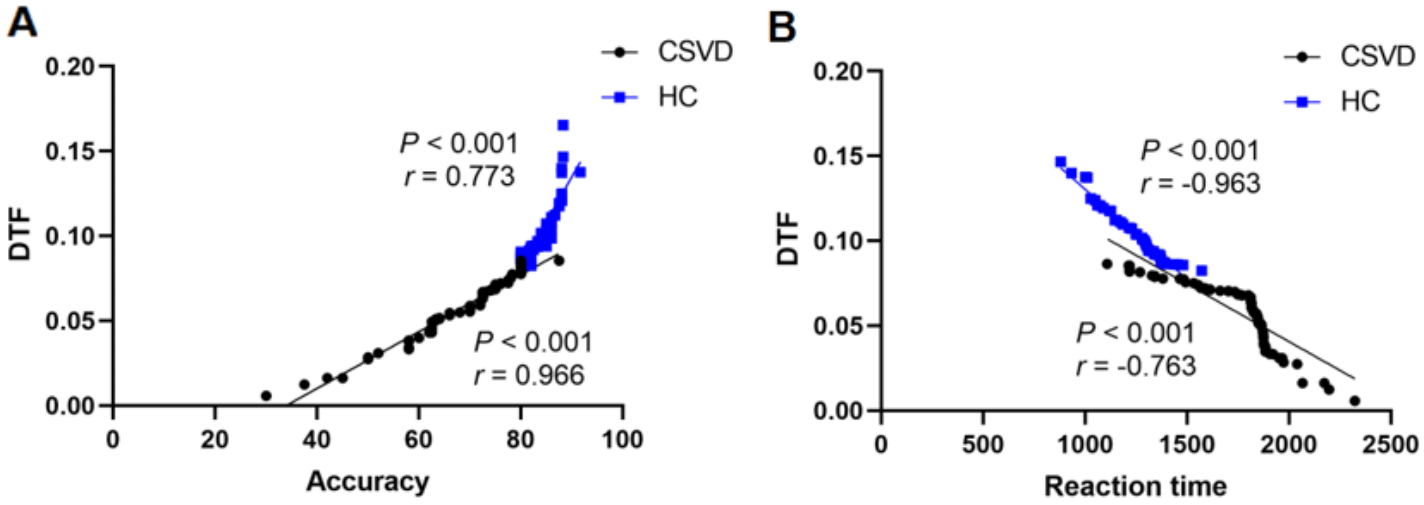

Figure 7

The correlations of WM behavior and frontal functional connectivity.

(A) Correlations between the accuracy of WM behavior and the functional connectivity strength in theta band of frontal region in the two groups. The HC group and CSVD group exhibited significantly positive correlation between the accuracy of WM behavior and the functional connectivity strength in theta band

of frontal region. (B) Correlations between the reaction time of WM behavior and the functional connectivity strength in theta band of frontal region in the two groups. The HC group and CSVD group exhibited significantly negative correlation between the reaction time of WM behavior and the functional connectivity strength in theta band of frontal region. WM, working memory; HC, healthy control; CSVD, Cerebral small vascular disease.