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Yijun Song *

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Research Article

Brain Network Controlling the Coding Period of Working Memory in Temporal Lobe Epilepsy: A Functional MR Imaging Study

Xin Zhang[1], Yuying Li[1], Dandan Guo[1], Yuan Yang[1], Lulin Zhang [1], Liping Pan [1], Yijun Song* [1,2]

[1] Department of General Medicine, Tianjin Medical University General Hospital, Tianjin, China,

[2] Tianjin Neurological Institute, Tianjin, China

***Corresponding Author:** Yijun Song, Department of General Medicine, Tianjin Medical University General Hospital and Tianjin Neurological Institute, Tianjin, China

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Abstract Objective:

Patients with temporal lobe epilepsy (TLE) often have working memory (WM) impairment. However, the mechanism of working memory coding is still unclear. This study aimed to uncover the mechanism of working memory coding period in TLE patients who have WM impairment. Methods: Functional magnetic resonance imaging (fMRI) data were collected from 37 patients with temporal lobe epilepsy (TLE) and 20 healthy control individuals. TLE patients were divided into a working memory impairment group (TLE-I) and a non-working memory disorder group (TLE-N) according to their performance of a delayed matching-to-sample (DMS) task, which is used to assess working memory. The data of the whole brain structure, resting state, and task state were collected. The active brain regions of the task state functional image data were compared as Region of interest (ROI), and the statistical differences of functional connectivity between groups were calculated. Finally, Pearson correlation analysis was performed to assess the statistical difference between functional linkage and behavioral performance using SPSS software. Results: The brain regions activated by the WM task coding were located primarily in the frontal cortex, parietal cortex, and occipital cortex. In the three groups, most of the brain regions inactivated during the process of task coding were concentrated in the brain regions involved in the default mode network (DMN). During the coding period, inactivation of the insula and hippocampus increased in TLE patients with behavioral abnormalities. The strength of functional connectivity within the parietal cortex was negatively correlated with behavioral accuracy. The strength of the functional connection between the frontal cortex and the occipital cortex was positively correlated with behavioral accuracy, but negatively correlated with reaction time (P less than 0.05). Conclusion: The task-positive networks in WM coding period were concentrated in the frontal-parietal-occipital networks, particularly in the brain networks dominated by the middle frontal gyrus, parietal cortex, and fusiform gyrus. The functional connections between the parietal cortex and the frontal occipital cortex, and the In review activity inhibition of the insular lobe, hippocampus, and other local brain regions may be related to the reduced task performance in WM coding period of TLE patients with WM impairment.

Key words: brain network; epilepsy; fMRI; working memory; coding period disorder

Introduction

Epilepsy is a common clinical disorder of the nervous system, with a global prevalence of approximately 5 percent [7]. Epilepsy is diagnosed when they present with any of the following conditions: 1. at least two unprovoked or reflex seizuresgreater than24 h apart; 2. one unprovoked or reflex seizure with the probability of another seizure, similar to the general recurrence risk (at least 60 percent), after two unprovoked seizures occurring within 10 years; or 3. with an epilepsy syndrome [7]. Temporal lobe epilepsy (TLE) is the most common type of intractable epilepsy in adults [8, 9], and is often associated with working memory impairment [10, 11].

Working memory is a cognitive process that involves storing, managing, and extracting information, which participated in almost all cognitive processes [1, 2]. Working memory can be categorized into different types. Visuospatial working memory (VWM) and verbal working memory are

the most commonly investigated type. VWM refers to the storage, immediate processing, and subsequent retrieval of visual information and spatial positions of objects [4]. Patients with TLE often experience VWM impairment [10, 11]. The delayed matching-to-sample (DMS) paradigm can be used to study VWM [5, 6]. DMS tasks can be used to assess WM processes time, including encoding, delay, and response time. The coding period is an indispensable first step in the entire process of WM. Region of interest (ROI) is a widely used technology in MRI. Researchers are required to select the region of interest as the seed point, extract the BOLD signal and calculate the corresponding functional connection network. In task-based fMRI, subjects are scanned whilst performing research-related tasks. This allows the investigator to calculate and analyze the activation of each brain region, allowing them to more intuitively describe the brain network of subjects In review during task execution. Compared with resting-state (RS) fMRI, task-based fMRI has greater and more direct advantages in determining the task relevance. It has also become one of the most commonly used imaging techniques in brain network research, especially in cognitive-related research. At present, growing evidence has demonstrated that brain networks can meet different working memory needs by adjusting the intra-network activation intensity and inter-network connection strength between brain regions. Recent studies have shown that, compared with healthy control groups, working memory impairment is related to a decrease in functional connectivity between the medial-frontal-insular-parietal network and the medial temporal network, including the bilateral middle frontal gyrus, inferior frontal gyrus, inferior parietal lobule, and thalamus [12-15]. However, relevant studies comparing the brain network mechanisms in TLE patients with WM impairment, TLE with no WM impairment, and healthy participants, using fMRI in the coding period has not been widely investigated or reported, to our knowledge. In this study, task fMRI combined with resting-state MRI region-of-interest (ROI) technology was used to study the brain networks involved in the coding period of VWM in patients with TLE.

2 Materials and Methods

2.1 Subjects and tasks:

Thirty-seven patients with TLE were recruited from the Department of Neurology, General Hospital of Tianjin Medical University, between 2018 and 2019 (Table 1). The inclusion criteria for all patients were as follows: 1) diagnosis according to the International League Against Epilepsy (22); 2) aged 18 or above; 3) Mini-Mental State Examination (MMSE) score greater than or equal to 24 (23); 4) no status epilepticus within 3 months of the experiment; 5) underwent 3T structural MRI and video EEG to confirm seizures in the temporal lobe; 6) taking antiepileptic drugs and were native Chinese; In review and 7) signed informed consent to voluntarily participate. Exclusion criteria were as follows: 1) unable to undergo MRI examination; 2) unable to complete the test or unwell at that time; 3) presence of alcohol dependency or drug use; 4) presence of other neurological or psychiatric disorders or severe systemic diseases; and 5) presence of other disorders that affect cognitive function. Twenty healthy volunteers were recruited as controls, using the following selection criteria: 1) matched with the patients' age, sex, education level, and other basic characteristics; 2) no history of brain trauma or major diseases, especially nervous system diseases, which may affect brain function and structure; 3) no drug or alcohol addiction or dependence; 4) good mental state; and 5) native Chinese. We applied ANOVA analysis to compare the demographic data in Table 2. This study conforms to the Declaration of Helsinki regarding the use of human subjects and was approved by the ethics committee of Tianjin Medical University General Hospital. Written informed consent was obtained from each patient during recruitment.

2.2 MRI data acquisition and pre-processing:

A Siemens Magnetom Trio Tim 3.0T MRI scanner and a 32-channel phased array surface coil were used for data acquisition. Before scanning, earplugs were inserted into the patient's ear, and their head was fixed with a matching sponge pad to reduce the impact of noise and head movement on the experimental data. The head coil was fixed on the patient's head, and the subjects were instructed to keep their eyes closed while remaining in a quiet and awake state, trying not to think, and keeping their head motionless. All subjects underwent thin sagittal T1 weighted imaging (T1WI) and RS fMRI. Parameters: plane echo imaging sequence was used in RS fMRI (repetition time [TR] 2000 ms; echo time [TE]: 30 ms; field of view: 220 mm × 220 mm; matrix: 256 × 256; layer thickness: 5 mm; number of layers: 20; flip angle: 90°; 300 frames in In review total); and thin-slice sagittal T1WI (3D pre-magnetized fast gradient echo sequence, TR: 1600 ms, TE: 2.52 ms; field of view: 256 mm × 256 mm; slice thickness: 1 mm; slice spacing: 0.5 mm), producing a total of 176 images per subject. DPARSF V2.2 (Data process assistant for RS fMRI) was utilized to pre-process the collected resting-state data using MATLAB 2009a. Head movement correction (Realign) was applied to ensure accuracy of the activation position; the epileptic group was shifted by greater than3 mm or rotated by greater than3°. To normalize the space, each subject's T1 structural image and their own functional image were used for registration, and the images after registration were normalized to the standard Montreal Neurological Institute coordinate system. A smooth kernel with a full width at half maximum of 6 mm × 6 mm × 6 mm was used for smoothing to further reduce the residual differences of individuals after standardization and to improve the signal-to-noise ratio.

2.3 DMS working memory:

Paradigm and grouping DMS, the classic working memory paradigm, was used in this study. Images of everyday objects from the Snodgrass photo library were used as visual stimuli. Subjects encoded in memory a set of stimuli and, after a delay of a few seconds, determined whether the probe stimulus that appeared matched one of the encoded memories (24). At the beginning of each test, a fixation point "*" appeared in the center of the screen for 0.5 s, indicating the start of the test. Four pictures from the memory sequence were then presented, each for 1 s, with a 13 ms interval between pictures. After the fourth picture disappeared, the screen showed a "+" symbol, reminding the subject of the delay period of 3 s. The detection picture was then displayed for 2.5 s. The subject needed to quickly and accurately determine whether the detection picture had appeared in the memory sequence. If the subject did not press the button within 2.5 s, the detection picture disappeared, and the test ended; the interval between the two tests was 4 s. This test procedure used the E-prime 2.0 block design. There were six blocks in total, and each block included ten of the above In review experiments. The probability of detecting the presence or absence of a picture was 50 percent. E-prime software records behavioral data, such as accuracy (ACC) and response time (RT). The ACC rate refers to the proportion of correctly judged tests during the trial; RT is based on the time it takes for the subject to respond correctly, i.e., the interval between the appearance of the probe picture and the subject's correct response (Figure 1). According to their ACC and RT scores (Table 1), the 37 patients with TLE were divided into the group without working memory impairment (TLE-N group, 17 cases) and the group with working memory impairment (TLE-I group, 20 cases). 2.4 fMRI data analysis The task state data were preprocessed, modeled, and statistically analyzed using spm12 on the MATLAB 2013a platform to obtain the activated brain area, inactivated brain area, and different brain areas in each group during the coding period. The ROIs were extracted using the RS software. The Pearson correlation coefficients of the average time series of each ROI and the average time series of the ROI were calculated. Fisher's r-to-z transform was used to transform the coefficients into Z values to improve normality. The calculation formula was $z = 0.5 \times \log[(1 + R) / (1 - r)]$, and the calculated value was the connection strength between two points in the brain area. Then, a single sample t-test was performed for each group, and the multiple comparisons of these analyses were corrected using the false detection rate method (P less than 0.05, two-tailed). Finally, we used SPSS software to conduct Pearson correlation analysis to assess the relationship between functional connection and behavioral performance. 2.5 Correlation analysis In order to explore the relationship between the functional connectivity of two

brain In review regions and working memory performance, we used the method of ROI for Pearson correlation analysis. We collected the Z values of functional links with statistical differences in the functional connections based on the region of interest, used SPSS software for correlation analysis, and calculated the partial correlation with age, sex, incidence frequency, and disease course as covariates. P less than 0.05 was significant, and used to indicate that there was a correlation. R values indicate the degree of correlation: r = 0 (none), r = 0 ~±0.3 (slight positive/negative), r =±0.3 ~±0.5 (real positive/negative), r =±0.5 ~±0.8 (significant positive/negative correlation), r =± 0.8 ~±1 (high positive/negative).

3 Results

3.1 Demographic and behavioral data:

There were no significant differences in sex, disease time, medication quantity, MMSE and MOCA among the three groups (P greater than 0.05, Table 2). There was a significant difference in RT and ACC among the TLE-I group, control group, and the TLE-N group (P less than 0.001), while there was no significant difference in RT and ACC between the control and TLE-N groups (P greater than 0.05). There was significant differences in RT and ACC of the TLE-I group (vs. control group and TLE-N group, P less than 0.001) (Table 2).

3.2 Intra group analysis of task state activated brain regions

We further analyzed the activated brain regions among three groups during the task coding period. As shown in Table 3 and Figure 2, the major activation brain areas in the control group were the bilateral fusiform gyrus, bilateral middle occipital gyrus, left inferior occipital gyrus, left superior parietal gyrus, bilateral middle frontal gyrus, bilateral caudate nucleus, and the left inferior frontal gyrus (P less than 0.001). While the main activated brain areas of TLE-N group subjects were the bilateral fusiform gyrus, bilateral supplementary motor area, bilateral middle frontal gyrus, bilateral inferior In review parietal gyrus, and the left triangular inferior frontal gyrus. The main areas activated in the brains of TLE-I subjects during the task coding period were the bilateral fusiform gyrus, bilateral middle frontal gyrus, bilateral supplementary motor area, bilateral superior parietal gyrus, and the left caudate nucleus (P less than 0.001). This data is presented in Table 3.

3.3 Inter group analysis of task state activated brain regions:

Compared with the control group, subjects in the TLE-N group showed less activation in the left middle frontal gyrus during the task coding period. While, the subjects in the TLE-N group showed with significant activation in the right middle frontal gyrus and left posterior cingulate (vs. control group, P less than 0.001, uncorrected, Table 4 and Figure 3). Whereas, in the TLE-I group, the activation was enhanced in the bilateral middle frontal gyrus, left medial superior frontal gyrus, bilateral precuneus, bilateral angular gyrus, right central posterior gyrus, left anterior cingulate, right posterior cingulate, left inferior occipital gyrus, left superior occipital gyrus, and right superior temporal gyrus (vs. control group, P less than 0.001) (Table 4 and Figure 3). Compared with the TLE-N group, subjects in the TLE-I group did not show weakened brain regions during the task coding period. The activation brain regions of TLE-I group were accumulated in the left middle frontal gyrus, bilateral caudate nucleus, right superior parietal gyrus, left inferior parietal gyrus, left superior marginal gyrus, right precuneus, bilateral talus fissure, and right lingual gyrus (vs. TLE-N group, P less than 0.001) (Table 4 and Figure 3).

3.4 Calculation of functional connections based on region of interest

3.4.1 Selection of seed points: The activated brain regions, obtained using the task state activation map, were analyzed using three groups of double sample t-tests and identified as the regions of In review interest (as shown in Table 5). The NMR data of the three subject groups were analyzed in order to assess the functional links between the regions of interest (Table 5).

3.4.2 Functional connections of different groups: Compared with the control group, the functional connections were weakened in the TLE-I groug between the right superior parietal gyrus and right middle frontal gyrus, left front buckle and right top gyrus, right central posterior gyrus and left superior occipital gyrus, right superior marginal gyrus and left caudate nucleus. Whereas, the functional connections were enhanced in TLE-I groug between the left superior marginal gyrus and left angular gyrus, the bilateral middle frontal gyrus, and the right precuneus and the right cerebellum (P less than 0.001) (Table 6 and Figure 4). Compared with the control group, the TLE-I group had no weakened functional connection, and the functional connections were enhanced between the right angular gyrus and right superior temporal gyrus, right superior marginal gyrus and right posterior central gyrus, right middle frontal gyrus and right lingual gyrus (P less than 0.001) (Table 6 and Figure 4). Compared with the TLE-N group, the TLE-I group had no weakened functional connections, and the functional connections were enhanced between the left angular gyrus and the right lingual gyrus, the right superior temporal gyrus, right angular gyrus and right superior temporal gyrus, right superior parietal gyrus, right middle frontal gyrus, and right lingual gyrus, right superior parietal gyrus, left superior occipital gyrus, left anterior cingulate band, and left superior occipital gyrus, and right precuneus and right superior parietal gyrus (P less than 0.001) (Table 6 and Figure 4).

3.4.3 Correlation analysis between functional connection strength and behavior: The correlation analysis of FC strength and ACC showed that the Z value of FC in the In review left angular gyrus and the left superior marginal gyrus was negatively correlated with ACC (r = -0.310, P = 0.019; Fig 5A). The Z value of the right middle frontal gyrus and the right lingual gyrus was negatively correlated with the ACC (r = -0.297, P = 0.025; Fig 5B). There was also a significant negative correlation between the Z value of the left and right superior temporal gyrus with ACC (r = -0.390, P = 0.003; Fig 5C). Additionally, a negative correlation between the Z value of the right corner gyrus and the right superior temporal gyrus with ACC was also presented (r = -0.335, P = 0.007; Fig 5D). Correlation analysis of FC and RT is shown in Figure 6E. The Z value of the FC between the right middle frontal gyrus and the right lingual gyrus was positively correlated with RT (r = 0.269, P = 0.043; Fig 6E)

4 Discussion

In this study, task fMRI combined with resting-state MRI ROI analysis was used to study the brain network involved in the coding period of VWM in patients with TLE. The results showed that some TLE patients had behavioral abnormalities in WM; their ACC was lower and their RT more prolonged than that of the control group. The brain regions involved in the WM coding period were mainly concentrated in the network of the frontal-parietal-occipital cortex, particularly in the middle frontal gyrus, parietal cortex, and fusiform gyrus. Inactivation of DMN-related brain regions plays an important role in WM coding. Inhibition of the insular lobe, hippocampus, and other local brain regions is related to the task performance of TLE patients in the WM coding phase. The FC between the parietal cortex and frontal occipital cortex is also closely related to WM task performance in patients with TLE. Previous studies have shown that refractory TLE can lead to a decline in cognitive function. For example, researchers collected learning and memory results of 1156 patients with early-onset TLE, as well as the behavioral data of 1000 healthy In review controls. They found that the memory score of patients with TLE was significantly lower than that of healthy controls, suggesting that the memory function of patients with TLE was impaired (23). In a study conducted in 2013, task tests were performed on TLE patients with unilateral hippocampal sclerosis as well as on healthy controls using the n-back paradigm. The results showed that the correct rate in the patient group was significantly lower than that in healthy subjects. At the same

time, data from number span and motor sequence tests were collected from the two groups, and it was found that TLE patients performed worse than healthy controls in all WM tasks, regardless of right or left hippocampal sclerosis (24). In this study, the DMS paradigm was used to test the participants' WM. We asked three groups of subjects to complete the WM task and collected the behavioral data. We found that compared to the control group, the accuracy of the TLE-I groups' executive paradigm decreased significantly, and the RT was significantly prolonged, which is consistent with previous research results. Recently, Roth et al. found that the frontoparietal network connections (including the supplementary motor area, parietal lobe, left inferior frontal junction, and middle frontal gyrus) were significantly activated in the process of new information update coding. In 2019, Kim conducted a meta-analysis on the sub-temporal processes of WM, revealing functional periods of the dorsal attention network (DAN) and the frontoparietal control network (FPCN) to be fundamental in WM. The results suggest that the coding stage involves multiple DAN regions - the bilateral and superior parietal lobe, but only one FPCN region - the left posteromedial prefrontal cortex. In addition to the DAN and FPCN, the bilateral supplementary motor area and left striatum were also involved [25]. Consistent with previous studies, we found that inactivation of DMN-related brain regions plays an important role in WM coding. We used the GLM model to test the data from the task state coding period after modeling, and found three groups of task-positive networks, the frontal-parietal-occipital region being the main brain area activated during the task in review coding period. In the control group, the brain areas activated during WM task coding were mainly concentrated in the following areas: 1] the frontal cortex: bilateral middle frontal gyrus and right inferior frontal gyrus; 2] the parietal cortex: left superior parietal gyrus; 3] the occipital visual cortex: bilateral fusiform gyrus, bilateral middle occipital gyrus, and left inferior occipital gyrus; 4] other brain areas, including the left supplementary motor area and the bilateral caudate nucleus, were also activated during coding. Consistent with previous research [25], our study shows that the prefrontal cortex plays a crucial role in WM processing. Previous studies have demonstrated the causal relationship between the dorsal lateral prefrontal cortex and WM through animal experiments [26, 27]. Furthermore, spatial WM preferentially activates the middle frontal gyrus (MFG) in the right hemisphere, and the activation occurs within 3–6 s after the beginning of the task and decreases after the disappearance of the task picture. In a meta-analysis, Daniel et al. found that compared with verbal WM, visuospatial WM was more effective in activating the right middle frontal gyrus (BA6 / 46) (28). Another study by Christophel et al. found that the prefrontal cortex reflects the working characteristics for guiding upcoming behavior and manipulating behavior conversion (29). In this study, a large number of frontal structures were found in the activated brain regions during the task coding period, which confirmed the role of the frontal cortex in the detection, collection, and manipulation of information during WM processing. Many studies have shown that the parietal cortex plays an important role in WM networks. The parietal cortex and the frontal cortex form a memory processing network involved in the process of WM. As early as 1993, researchers speculated that the parietal lobe participates in the activation of WM, and that the posterior parietal lobe is responsible for the extraction and replication of spatial information (30). In 2007, a study investigating the role of the left intraparietal sulcus (IPS) in attention during visual WM tasks showed that the IPS regulates attention by connecting different neural networks across different visual short-term memory tasks. In the process of sequential coding, the left IPS plays an important role in the process of in review identity coding, and also has priority FC with the right temporal, subparietal, and medial frontal regions involved in facial detail processing. These findings suggest that the parietal cortex connects external attention and internal information coding through other brain regions during WM (31). Ren et al. used voxel-based morphometry (VBM) and resting-state functional connectivity analysis to study the relationship between goal ability and spatial WM, regional gray matter density, and intrinsic FC. They believed that WM was related to the structure and functional organization of brain regions involved in the ventral pathway (occipitotemporal region), while the dorsal pathway (frontal-parietal region) was related to spatial WM and the capacity of WM (32). The present study also presents results that suggest that the parietal cortex is involved in WM activity. Regarding the role of the visual cortex in WM, some studies have confirmed that it is activated during the WM coding process (33, 34). For example, Van et al. studied the specific mechanism of visual cortex participation in WM using non-invasive brain stimulation data. They used single-pulse transcranial magnetic stimulation to stimulate the occipital cortex and found that it affected WM consolidation, suggesting that the early visual cortex plays a continuous role in maintaining spatial information (35). Another study by Galeano et al. combined fMRI connectivity analysis with behavioral modeling and found that higher occipitoparietal connectivity was related to a higher average accuracy of behavior [36]. These findings suggest that the occipital cortex is not only involved in the WM coding stage, but is also more likely to participate in WM processing in the form of parietal-occipital network connections. It is therefore not surprising that in this study, the occipital cortex was activated when pictures were encoded into WM, given that the fusiform gyrus is close to both the fusiform face area and the occipital region V4 / V8 for color recognition of faces and pictures [37], and the middle occipital gyrus is close to the occipito-facial region [38]. The results of this study support the view that the visual cortex participates in WM as a function of recognition, collection, and transmission of information. In review

In the control group, the main brain areas that were inactivated during the WM task were the bilateral medial superior frontal gyrus, bilateral middle cingulate gyrus, bilateral angular gyrus, superior marginal gyrus, left posterior central gyrus, and the bilateral middle temporal gyrus. Most of these brain areas are a part of the DMN, which includes the medial frontal lobe, cingulate gyrus, and bilateral parietal cortex. This result is consistent with the results of extensive research on WM [39]; in the process of WM coding, DMN brain areas are in a state of inhibition, and negatively correlated with the activation of the central executive control network, frontal-parietal network, and other executive task networks. For example, a study by Zuo et al. that evaluated the cognitive load and network role of WM found that under a higher cognitive load [2-dorsal], the FPCN, DAN, and salience network [SN] showed significant activation and a positive correlation, while the DMN showed the opposite pattern, that is, significant deactivation and a negative correlation [39]. This is consistent with the findings within the control group in this study. In previous studies, the DMN has been demonstrated to be the basis of the cognitive network in the resting state. In the WM process, especially when WM information is updated during the coding period, the FPN, DAN, SN, and other networks are activated due to external attention and internal information collection, whereas inactivation of DMN-related brain regions inhibits stimulation signals unrelated to information itself, in order to ensure that execution of the WM coding process is successful [40]. For example, Stretton et al. used the "n-back" paradigm to study the network of 17 TLE patients with a lifelong emotional diagnosis, 31 TLE patients without mental history, and 30 healthy volunteers. The results showed the frontal-parietal WM network and the typical DMN areas were activated in each group [41]. However, compared to the other two groups, there was a higher level of inactivation in the right insular lobe and left hippocampus in the WM group. The insular lobe, an important node of the SN and FPCN, which has been shown to be a control and command center in previous studies, participates in neuropsychological processes such as consciousness, cognition, perception, attention, and risk experience. Therefore, the inactivation of insular lobes in this study may be related to the poor performance of WM subjects in the task. The In review importance of the hippocampus in memory is well known, and it is often mentioned in WM research, especially in studies of TLE patients. For example, a study by Stretton et al. compared the WM network activity of 30 patients with unilateral hippocampal sclerosis and 30 healthy controls, and determined that although no obvious hippocampal activation was found in any group during the active task, with the increase of task demand, the hippocampus gradually became inactive, which was related

to better behavioral performance [42]. In our study, even though the task load of the three groups was the same, inhibition of the hippocampus was only observed in the TLE-I group. This suggests that individuals in the TLE-I group experience inhibition of the hippocampus as the relative task load increases. Compared with the control group, activation of the right middle frontal gyrus increased in the TLE groups. Activation of the left middle frontal gyrus was higher than in the TLE-I group than in the control or TLE group. The middle frontal gyrus has been frequently mentioned as an important node in previous WM studies [43]. In fact, the right middle frontal gyrus is a more important brain area than the left middle frontal gyrus for WM processing in TLE patients [44]. Considering the behavioral differences among the three groups, the activation of the right middle frontal gyrus was preferentially enhanced in the TLE group, while the contralateral middle frontal gyrus was highly enhanced as a compensation mechanism in the TLE-I group. Compared to the other two groups, the visual cortex of the TLE-I group was more significantly activated. As the main sensory system for WM to receive information, information coding and inclusion of the visual cortex are crucial to visual-spatial WM processing [45]. Therefore, in the TLE-I group, the occipital cortex may be activated for sensory compensation when WM task performance is poor. In contrast to the previously identified WM brain network, the bilateral cerebellum [Crus I area] was more significantly activated in the TLE-1 compared to control groups. In fact, previous studies have shown that the cerebellum, in addition to its extensive cognitive-motor function, is also involved in cognitive processing, especially the Crus I, II, and lobular VI areas [45]. In this study, we only found activation of the Crus I In review region. The left superior temporal gyrus was activated during WM task performance. Previous studies also found that the superior temporal gyrus was responsible for encoding the information and processing the shape of the object during WM processing, and that it participated in the neural activity that occurs during the WM coding period. In addition to the new brain regions proposed, the medial prefrontal cortex, parietal cortex, and other brain regions, were more activated in the TLE-1 group than in the control and TLE-N groups. When memory function decreases due to epilepsy, the frontoparietal network and attention network are activated to supplement this functional damage. A study of the frontoparietal attention network found that in the decline of age-related WM performance, the DAN was also involved in the compensation of brain regions [46]. We identified the brain regions with significant activation differences between our three groups, and used these areas as ROI in assessing functional connections. Our results showed changes in FC in the case group, indicating the presence of changes in the neural network of TLE patients. We found a statistically significant connection between the frontal-parietal-occipital cortex, consistent with previous studies. The bilateral middle frontal gyrus, connections between the middle frontal gyrus and parietal cortex, and connections between the middle frontal gyrus and occipital cortex were enhanced in the TLE group, indicating the central role of the frontal cortex in the WM coding period. A study by Stretton et al. used the middle frontal gyrus and superior parietal lobe to assess FC for a given ROI in order to determine the mechanism underlying WM, and found that the FC of the VWM in TLE patients changed [47]. The resting-state network, composed of the frontal, parietal, and occipital regions, is an important neural basis for WM processing. When the neural nodes are damaged by disease discharge, the brains of TLE patients need to enhance the relevant functional connections and trigger new functional connections as a complementary mechanism to compensate for poor WM performance. In this study, the effective connection Z value was calculated based on the task ACC In review and RT scores of the three groups. There was a strong correlation between the intensity of the ACC connection and WM processing. In addition, the Z value of the FC between the right superior temporal gyrus and bilateral angular gyrus was negatively correlated with the ACC of the subjects performing WM tasks, suggesting that the connection between the superior temporal gyrus and the parietal lobe was related to the memory process. As early as 1995, Thompson KH and other scholars used positron emission tomography to study WM, which showed that the superior temporal gyrus was activated in the WM coding and delay stages, indicating that it was related to the WM process [48]. In 2019, Ren et al. found that the significant difference in the superior temporal gyrus was positively correlated with its regional gray matter density, based on VBM analysis, suggesting its correlation with WM. In the correlation test, the Z value of the FC between the right middle frontal gyrus and the right lingual gyrus was positively correlated with RT, and negatively correlated with ACC. Activation of the lingual gyrus in the WM coding period and its connectivity with other brain regions has been proposed in previous studies [49]. Some studies have suggested that the parietooccipital junction is related to the accuracy of WM. For example, Yang et al. assessed the resting-state brain network of TLE patients with cognitive impairment, and found that the FC between the medial visual network and the left frontoparietal network in the patient group was significantly lower, and was also related to the MoCA score, indicating that the decrease in the connection strength between the visual cortex and the frontoparietal network was related to cognitive impairment [51]. In this study, we found a correlation between the FC of the frontal cortex and occipital cortex and the behavioral data, which suggests that the network connectivity between the frontal cortex and occipital cortex plays an important role in the process of WM coding. Importantly, the connectivity of the TLE-I group was stronger than that of the other two groups. Therefore, it is reasonable to speculate that there is a compensatory response that occurs in the process of information coding through the sensory system in patients with WM damage. In review

This study has some limitations. First, the sample size of the subjects in this study was small; more stable and accurate results may be obtained by increasing the sample size. Second, TLE can be divided into left, right, and bilateral subgroups according to the origin of the lesions. Therefore, the effects of different hemispheric lateralization on visual WM and the brain networks of TLE patients need to be further assessed in these different subgroups. In the future, the sample size should be increased, and subgroup assessments should be added to achieve more detailed experimental results. Third, occipital cortex activation was found during the editing period of working memory. However, to what extent these activations are related to the visual presentation and processing of the data is unknown. We will add the comparison of brain networks in the rest condition in the future.

5 Conclusion

Some TLE patients showed behavioral abnormalities in WM; their ACC decreased, and RT was prolonged. The task-positive networks in the WM coding period were concentrated in the frontal-parietal occipital network, primarily in the middle frontal gyrus, parietal cortex, and fusiform gyrus. Therefore, activity inhibition of the insular lobe, hippocampus, and other local brain regions may be related to the task performance during the WM coding period of TLE patients. The functional connections between the parietal cortex and the frontal occipital cortex may be related to the task performance of WM in TLE patients.

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Ethics approval and consent to participate

Ethics approval and consent to participate: This study was approved by the ethics committee of Tianjin Medical University General Hospital, and informed written consent was obtained from all participants. All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Competing Interests: The authors declare that they have no competing interests. In review.

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