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# *Verbal and Spatial Working Memory Impairment in Mild Cognitive Impairment Patients with Liver-Qi Depression Syndrome: An Event-Related Potential Study*

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***Abstract:*** This study delves into the investigation of verbal and spatial working memory impairments in mild cognitive impairment (MCI) patients, focusing particularly on those with liver-qi depression syndrome (LQDS). Event-related potential (ERP) techniques were employed for this investigation. Twenty-six healthy young subjects were recruited for an ERP experiment to validate the Chinese version of the Letter-Number n-back experimental paradigm. The study also involved the selection of MCI patients with LQDS (MCI group) and normal middle-aged and older adults (NC group) through questionnaire surveys, with 14 participants in each group. The ERP technique explored the P2 and P300 components related to verbal and spatial working memory in the three groups (MCI patients with LQDS, NC group, and youth group) under various tasks. Results showed that as the task load increased, all three groups displayed a significant decrease in accuracy and reaction time. The MCI group demonstrated the lowest accuracy and reaction time, while the youth group exhibited the highest values. Additionally, P300 latency was observed to be shorter in the MCI group compared to the NC and youth groups, suggesting a potential sensitivity index for detecting early decline in MCI patients with LQDS. In conclusion, this study highlights the overall cognitive function decline in MCI patients with LQDS, with the most prominent changes observed in behavioral responses. The results suggest that P300 could serve as a potential marker for detecting the early stages of decline in this population.

## 1. Introduction

In recent years, there has been increased focus on the impact of emotions on working memory in the context of mild cognitive impairment (MCI) [1-2]. Studies have indicated that mental conditions such as anxiety and depression are associated with increased risk of progressing from MCI to dementia [3]. According to traditional Chinese medicine, chronic mood disturbances and stagnation

of liver qi can lead to cognitive decline. Therefore, it is clear that sustained emotional depression is a critical factor in initiating MCI.

Working memory is crucial for cognitive processes, such as learning and reasoning [4]. Impairments in working memory have been observed in people with MCI, indicating declining memory[5]. More research is needed to improve diagnostic criteria and develop effective prevention and treatment strategies. The role of the liver in MCI development remains unclear. Traditional Chinese medicine offers insights into cognitive symptoms of MCI, but research on working memory in MCI patients is limited[6]. Comprehensive memory processing models and advanced techniques are necessary for further study.

The event-related potential (ERP) technique provides insights into cognitive changes within individuals[7]. EEG signals can be divided into components corresponding to different cognitive stages, revealing information processing and psychological reactions[8]. The ERP technique is valuable due to its objectivity, temporal resolution, and cost-effectiveness in studying brain cognitive function [9]. It can uncover alterations in working memory among patients with MCI of the LQDS subtype, shedding light on the liver's potential involvement in MCI pathogenesis.

Baddeley's cognitive model of working memory suggests 3 sub-components, each with distinct functions[10]. Aging causes decline in verbal and spatial working memory. The extent of this decline and its link to LQDS due to prolonged negative emotion require exploration [11]. This study utilizes event-related potential technique to explore the mechanism of verbal and spatial working memory, in order to identify a sensitive index for early identification of MCI patients with LQDS.

## 2. Materials

### 2.1. Subjects

The study involved three participant groups: youth, MCI, and control. The youth group comprised 26 undergraduate and postgraduate students (13 females, 13 males) with an average age of 15.25±2.65 years. The MCI group consisted of 14 middle-aged and elderly individuals (7 females, 7 males) diagnosed with MCI and LQDS, receiving treatment at the First Affiliated Hospital of Nanchang University between January 2021 and July 2022. The control group included middle-aged and elderly individuals with normal cognitive function, matched 1:1 to the case group based on age (±2.5 years), gender, educational level, and time of investigation. Ethical approval was obtained from the Ethics Committee of First Affiliated Hospital of Nanchang University, and all participants provided written consent. The diagnostic criteria for MCI were based on widely accepted European AD Association criteria [12], encompassing patient or family-reported cognitive impairment, decline in cognitive function within the past year, confirmed cognitive impairment via clinical evaluation, intact activities of daily living, and the absence of dementia.

### 2.2. Inclusion Criteria

Inclusion criteria encompassed specific age ranges for each group. The youth group included individuals aged 19-28 years, while the middle and elderly group contained individuals aged 45-65. All participants in the three groups were native Chinese, right-handed, possessed unaided or corrected visual acuity of at least 1.0, and exhibited normal hearing and language functions, either alone or after correction, meeting the experiment's requirements.

#### 2.2.1. MCI Group

Participants in the MCI group exhibited objective memory impairment while maintaining normal

cognitive function. The group fulfilled the following criteria: total Mini-Mental State Exam (MMSE) score within the normal range, comprehensive Montreal Cognitive Assessment (MoCA) score ranging from 19 to 25, Activities of Daily Living (ADL) score below 26 points, Geriatric Depression Scale (GDS) score between 2 and 3 points, and a liver qi stagnation syndrome rating scale score of at least 6 points.

#### 2.2.2. Control Group

The control group exhibited normal cognitive function across all tests. Specifically, this group's criteria encompassed a total MMSE score within the normal range, a total MoCA score equal to or exceeding 26, intact social adaptability, an ADL score below 26 points, and a GDS level 1 score.

### 2.3. Exclusion Criteria

Participants were excluded if they met any of the following criteria: (1) MMSE score < 14 points; (2) presence of limb or other functional limitations hindering examinations; (3) history of cerebrovascular or nervous system diseases; (4) severe lesions in vital organs potentially impacting brain or cognitive function; (5) presence of mental disorders or conditions impeding cooperation with investigation and assessment; (6) recent use of cognitive-function-affecting drugs within the last 60 days; (7) unreliability in the source or content of information.

## 3. Methods

### 3.1. Questionnaires

A custom-tailored questionnaire has been created to collect information from participants, which includes details such as gender, age, educational background, medical history, and other pertinent information.

MoCA (Montreal Cognitive Assessment): A cognitive screening tool.

MMSE (Mini-Mental State Exam): A widely used cognitive function assessment.

ADL (Activities of Daily Living): A measure of an individual's capability to independently perform daily tasks.

GDS (Geriatric Depression Scale): A tool for assessing depression in elderly individuals.

Liver Qi Stagnation Syndrome Evaluation Scale: Employed to evaluate the presence and severity of liver-qi stagnation syndrome.

### 3.2. ERP experimental design

#### 3.2.1. Stimulus Material

N-back task was chosen as experimental paradigm. The stimuli consisted of Arabic numbers from 2 to 5, presented as white text on a black background. Each number appeared randomly in four positions, including above and below the two diagonal lines of the horizontal and vertical axes.

#### 3.2.2. Stimulus Procedures

This N-back consisting of 96 trials. In the 0-back task, participants determined if the displayed number matched a target number. The target number was presented for 500ms, followed by a response time of 3500ms. For the 1-back and 2-back tasks, participants had to determine if the current number matched the one seen one or two steps earlier. They used the "F" (left index finger)

and "J" (right index finger) keys for matches and non-matches, respectively. Instructions were either verbal or spatial, requiring participants to memorize the number or its position. Matching and non-matching proportions were 50% and randomized.

### 3.3. EEG recording

40-lead Ag/AgCl electrode cap was worn, with mastoid averages as references [13]. Electrodes were placed for HEOG and VEOG recording. The analog filter spanned 0.05 to 100 Hz, sampling at 1000 Hz. Impedance was kept below 5 kΩ. EEG and behavioral data were concurrently recorded.

### 3.4. Statistical Analysis

#### 3.4.1. Data Entry and Preprocessing

EEG data underwent offline processing using NeuroScan 4.5 software, with VEOG and HEOG corrections and low-pass 24Hz digital filter. Automated artifact exclusion was set for amplitudes exceeding ±100μV, and analysis covered 200ms pre-stimulation and 800ms post-stimulation epoch. Event-related potentials were observed at FZ, CZ, and PZ electrode points, with N1, P2, and P300 average amplitudes measured. Data were exported to files.

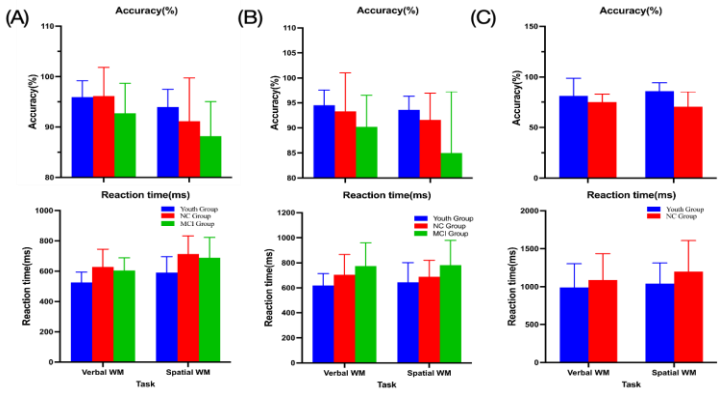
#### 3.4.2. Data Analysis

Data were processed using SPSS 22.0 software. Repeated-measures ANOVA assessed average amplitudes of event-related potential components. The experimental group had three levels: MCI group, normal middle-aged and elderly control group, and young group. Intragroup factors included electrode point and task type. Significance was determined at $P<0.05$.

## 4. Results

### 4.1. Behavioral Results

Results revealed significant main effects for both group ($F=4.627$, $P=0.013$) and task type ($F=21.253$, $P=0.000$), with an interaction between them ($F=3.609$, $P=0.033$). Accuracy in verbal working memory was significantly higher than spatial working memory, with the youth group demonstrating the highest accuracy and the MCI group exhibiting the lowest. The MCI group showed a significantly greater decline than the youth group, while no significant distinctions were found between the NC group and either the MCI group or the youth group (Figure 1A).




(A) 0-back, (B) 1-back, (C) 2-back.

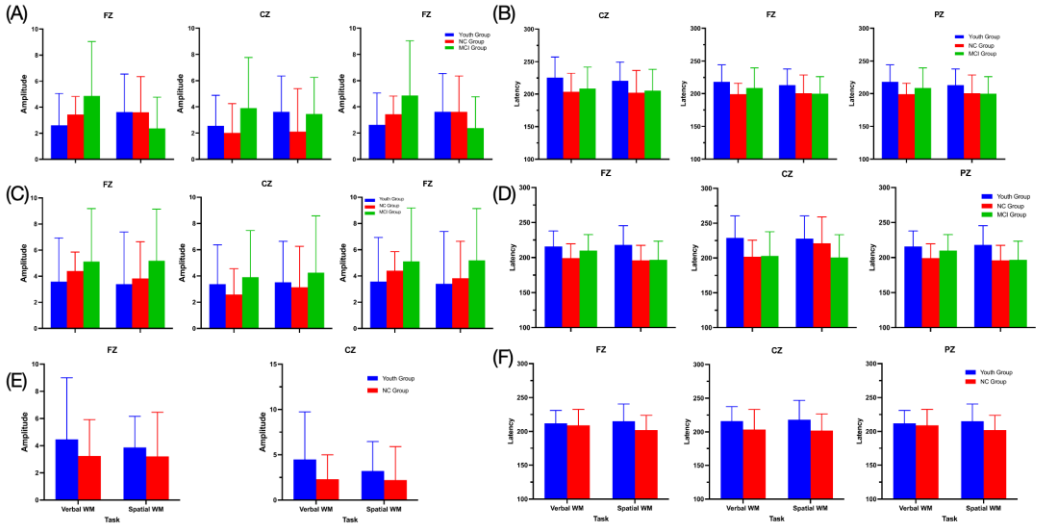
Figure 1 Accuracy and reaction time under the N-back task.

The results showed a significant main effect for group (F=6.968, P=0.0025) and task type (F=6.625, P=0.013). However, there was no significant interaction between group and task type. Accuracy was consistently higher in verbal working memory tasks compared to spatial tasks. Overall, the MCI group had the lowest accuracy (Figure 1B). There was a significant main effect for the group (F=5.178, P=0.009), but no main effect for task type or interaction between group and task type. Further analysis showed that the MCI group had shorter response times compared to the youth group in both verbal and spatial tasks.

A substantial group effect for the correct rate ($F$=3.769, $P$=0.000<0.01), while no significant main effect was observed for the other variables. Moreover, no interaction was noted between group and task type. Further analysis demonstrated that the correct rate in the NC group was lower than that in the youth group, regardless of whether it was verbal or spatial tasks (Figure 1C).

## 4.2. Results of ERP Component Analysis

The ERP responses to matching and mismatching stimuli eliciting correct responses were analyzed under task types and three task loads, yielding identical time histories for six ERP components. P2 exhibited more pronounced induction in the frontal scalp region, while P300 was more evident in the posterior scalp area. P2 and P300 demonstrated significant effects on electrode points ($P$<0.05). The maximum amplitude of P2 was observed at electrode F2, while P300's maximum amplitude was localized at electrode PZ.




(A)amplitude under the 0-back, (B)latency under the 0-back, (C)amplitude under the1-back, (D)latency under the 1-back, (E)amplitude under the 2-back, (F)latency under the 2-back. P2 latency of MCI and NC groups was shorter than that of the youth group (P<0.05).

Figure 2 Average P2 amplitude and latency under the N-back task.

(1) Results for 0-back Task Comparison

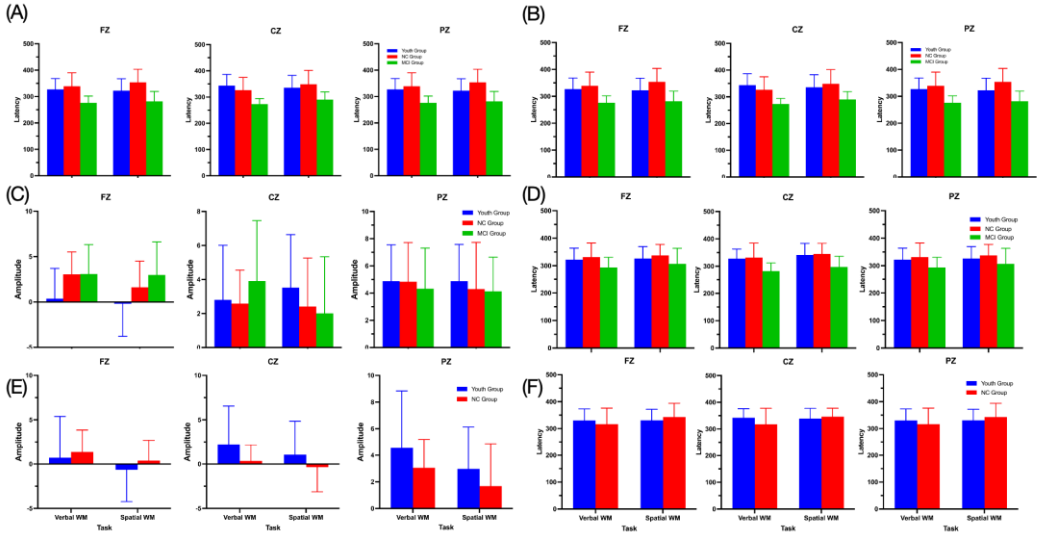
The results showed a significant main effect of electrode points (F=17.081, P=0.000) and an interaction between electrode points and task type (F=4.319, P=0.027). Other main effects and interactions were not significant. Further analysis revealed that FZ had the highest P2 amplitude for both verbal and spatial tasks across all groups (Figure 2A). P2 latency was analyzed using a three-factor repeated-measures ANOVA, which showed significant main effects of group (F=5.289, P=0.007) and electrode (F=5.269, P=0.000), but no main effects related to task type or other interactions. Further analysis showed that P2 latency was shorter in the MCI and NC groups compared to the youth group, with no significant difference between the two groups (Figure 2B).

(2) Results for 1-back Task Comparison

The findings showed a significant main effect for electrode points (F=16.053, P=0.000) and an interaction between electrode points and groups (F=3.379, P=0.025). The processing of P2 in the MCI group may involve different sources in the brain compared to the NC and youth groups (Figure 2C). The results also revealed significant main effects for group (F=8.701, P=0.000) and electrode (F=51.231, P=0.000), with no main effect for task type or interaction between group and task type. P2 latency in the MCI and NC groups was shorter than in the youth groups (P<0.05). However, there was no significant difference between the MCI group and the NC group (Figure 2D).

(3) Results for 2-back Task Comparison

The mean amplitude of P2 at the frontal scalp during the 2-back task was analyzed using a three-factor repeated-measures ANOVA. The results showed a significant main effect for electrode points (F=9.481, P=0.001), with no significant main effects or interactions. The maximum P2 amplitude in both groups was found at electrode FZ (Figure 2E). P2 latency was examined using a three-factor repeated-measures ANOVA. The findings showed significant group effects (F=5.099, P=0.027) and a main effect for electrode points (F=12.649, P=0.000), with no other main effects or interactions. The latency of P2 in the NC group was shorter than in the youth group (Figure 2F).




(A)amplitude under the 0-back, (B)latency under the 0-back, (C)amplitude under the1-back, (D)latency under the 1-back, (E)amplitude under the 2-back, (F)latency under the 2-back.

Figure 3 Average P300 amplitude and latency under the N-back task.

The P300 latency in the MCI group was shorter compared to the NC and youth groups across all task loads.Further analysis revealed that the maximum amplitude of P300 was localized at electrode PZ regardless of task type. Significant P300 induction was observed in the anterior scalp for both the MCI and NC groups, but not in the youth group. The average amplitude for verbal tasks was higher than for spatial tasks. The latency of P300 was shorter in the MCI group compared to the NC group, and longer in spatial tasks compared to verbal tasks.Under the 1-back task, the maximum amplitude of P300 was localized at electrode FZ. P300 induction was observed in the MCI and NC groups at the FZ point, but not in the youth group. The average amplitude induced by the anterior scalp was higher in the MCI group compared to the NC group. There were no significant effects or interactions for the P300 latency.For the 2-back task, the maximum amplitude of P300 was localized at electrode FZ under both verbal and spatial task conditions. The P300 latency induced by the NC group was shorter than that of the youth group. However, there were no significant effects or interactions for the P300 latency (Figure 3).

## 5. Discussion

Working memory is a crucial cognitive system for temporarily storing and manipulating information during tasks that require limited cognitive resources. It consists of spatial and verbal components, with spatial working memory aiding in navigation and interaction with the environment, while verbal working memory is essential for language and logical reasoning. Verbal working memory deficits are often observed in individuals with Mild Cognitive Impairment (MCI), indicating early cognitive dysfunction [15]. Spatial working memory decline may precede traditional memory deficits in MCI and may be more pronounced with age [16]. Spatial working memory tasks exhibit lower accuracy compared to verbal working memory tasks, suggesting age-related degenerative processes may have a greater impact on spatial working memory [17].

Event-Related Potentials (ERPs) capture the brain's responses to specific stimuli, providing dynamic insights into cognitive processing [18]. The appearance of the P2 component signifies attention engagement after visual stimulus presentation [16]. The study revealed increased P2 latency and decreased amplitude in spatial working memory tasks, indicating a decline in spatial attention ability in MCI patients. P2 activations were observed in all subject groups during both verbal and spatial working memory tasks, supporting the idea that age-related impairment in visuospatial ability may manifest before deficits in verbal skills [14]. P2 is linked to sensory responses to visual stimuli, and significant P2 were observed in all three subject groups during verbal and spatial working memory tasks, indicating substantial brain activity with numerical stimuli. Analyzing P2 variations across different task conditions provided insights into the working memory of MCI individuals with LQDS. Middle-aged and elderly participants in both groups efficiently allocated attention resources, possibly influenced by their attitudes and perceptions over time. In contrast, the younger group may have a relatively indifferent stance towards temporal influences, which could affect attentional resource allocation.

The P300 waveform consists of components like P3a and P3b [19]. P3b is elicited by target stimuli relevant to the task, while P3a arises from irrelevant sporadic stimuli. In elderly individuals or those with frontal cortex impairments like MCI/AD, P3a responses may be more common due to difficulty forming and maintaining memory templates. The study found a significant difference in P300 latency between the MCI group, NC group, and the youth group. The shorter latency in the MCI group suggests differences in information processing, while the NC and youth groups exhibited P3b responses. This points to a cognitive processing decline in individuals with MCI and suggests P300 as a valuable marker in diagnosing MCI/AD. This study provides valuable insights into working memory differences across age groups and cognitive states, emphasizing the importance of assessing spatial and verbal working memory abilities. Understanding these differences aids in early detection and characterization of cognitive decline, benefiting diagnostic and intervention strategies. The study also highlights the utility of ERPs, particularly the P2 and P300 components, in investigating cognitive processes associated with working memory tasks.

While this study focused on n-back paradigm using numbers to assess working memory refresh functions, it didn't investigate other components and mechanisms related to working memory retention. Future research should explore these aspects using different paradigms. The broad age span of the elderly participants and the small sample size limited the analysis of menopause effects on cognitive function across different ages. Future studies should include larger sample sizes and diverse age groups to examine the impact of menopause on cognitive function. This study provided initial insights into the ERP characteristics and mechanisms of spatial and verbal working memory decline in MCI patients with LQDS. However, future research could investigate relationship between LQDS, spatial and verbal working memory, and brain aging by integrating emotional interventions, cognitive training, and exploring neural mechanisms involved.

## 6. Conclusions

Spatial memory is more impacted by normal aging and MCI. Enhanced attention in older adults and MCI with LQDS suggests compensatory mechanisms. Cognitive decline in MCI with LQDS is linked to notable behavioral changes, with P300 as an early indicator of emotional dysregulation-related decline. Reduced memory capacity due to LQDS may underlie the decline in verbal and spatial memory, supporting hypothesis of emotional dysregulation accelerating working memory decline, enriching traditional Chinese medicine's understanding of cognitive decline.

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