

## Review Article

# Recent progress in migraine and cognitive disorder

Song Xiao-Wen, Cao Lin, Chen Jin-Bo\*, Wu Xin-Tong

Department of Neurology, The Affiliated Hospital of Binzhou Medical University, Binzhou, China

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**\*Correspondence:**

Dr. Chen Jin-Bo,

E-mail: [chenjinbo6720@126.com](mailto:chenjinbo6720@126.com)

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### ABSTRACT

Migraine is a chronic neurovascular disease characterized by recurrent unilateral headache, which induces incapacity. At present, there are many methods to evaluate cognitive function, and the cognitive function scale is commonly used. Recently, event-related potentials, resting state functional magnetic resonance imaging and other new technologies have been widely used to assess the cognitive function of migraine patients because of their high temporal resolution and high spatial resolution. In this paper, we can overview that the research progress of the relationship between migraine and methods of evaluate cognitive function.

**Keywords:** Cognitive function, ERP, FMRI, Migraine, Reviews

## INTRODUCTION

Migraine is a paroxysmal neurological disorder affecting up to 12% of males and 24% of females.<sup>1-4</sup> Prevalence is highest during an individual's peak productivity years, between the ages of 25 and 55, where it has significant impact on daily life with substantial functional impairment that include both physical and emotional ramifications.<sup>2</sup> The disease is principally characterized by recurrent attacks of unilateral headache that typically last 4 to 72 hours, associated with other neurological symptoms in addition to pain, such as nausea, photophobia, phonophobia, osmophobia and fatigue as well as numerous disturbances in autonomic, mental, sensory and motor functions.<sup>2,5</sup> The cumulative effect of long-term repeated attacks of migraine can lead to changes in brain structure and function, as well as the possible impact of cognitive function. The cognitive function of migraine has attracted more and more attention of the researchers, but there are many research methods, the methods are not consistent and the results are not consistent. This article is reviewing the effects of migraine on cognition.

## POSSIBLE MECHANISMS OF THE COGNITIVE FUNCTION OF PATIENTS WITH MIGRAINE

Despite all the progress that research has accomplished, the neural mechanisms underlying the onset and maintenance of migraine attacks are poorly understood. The main pathophysiological theories are cortical spreading depression (CSD) and trigeminal nerve vascular activation. Cerebral white matter ischemia and nerve fiber cell injuries are caused by these mechanisms, which include cerebral diffusion inhibition, hemodynamic changes, vascular spasm, and inflammatory response. Signal changes in the frontal cortex, deep brain white matter, and posterior white matter of migraine patients have been recorded through magnetic resonance imaging (MRI).<sup>7,10</sup> Diffusion-weighted MRI was used to study the white matter in the right frontal lobe of patients with migraine, and the results showed that the average diffusion coefficient increased. Advanced neuroimaging techniques reveal the functional and structural changes in certain pain processing networks of migraine patients, which may reflect the pathophysiological changes in migraine to a

certain extent.<sup>8</sup> Fiber tracking imaging reveals the other regions of the brain and the brain's pain-associated networks, such as the orbitofrontal cortex, insula, thalamus, and dorsal midbrain. Brain structural changes in patients with migraine may reflect brain plasticity change, a maladaptive central nervous system, and white matter collapse.<sup>9</sup> In Reference, CSD was inferred to be either single or originating from the primitive visual cortex.<sup>7</sup>

The spreading of the ventral and dorsal visual pathway to the posterior parietal cortex and temporal lobe as well as the movement of the language center are believed to cause color prosopagnosia, retrograde amnesia, dyslexia, movement disorders, distraction, and cognitive impairment; aura duration may also affect the frequency and type of these cognitive dysfunctions.<sup>7,10</sup>

Brain imaging changes in patients with migraine are mainly located in the frontal cortex and deep white matter. The other sections of the brain, such as the stem, insular lobe, and other structures of the hippocampus, are currently being studied. MRI imaging studies on several migraine patients showed that the probability of cerebral white matter lesions occurring in the frontal lobe in patients with migraine is higher than that in the controls; this phenomenon may be the pathological basis of the decline in the cognitive function of patients with migraine.<sup>11</sup>

#### **MIGRAINE AND COGNITIVE ASSESSMENT SCALE**

Common migraine auxiliary assessment scales include visual analogue scale, migraine disability assessment scale, headache impact assessment scale (HIT-6), and simple screening questionnaire (ID migraine). These scales are mainly used to screen and evaluate the severity of migraine, but no unified comprehensive assessment scale for the cognitive function exists. Migraine is mainly manifested as a mild cognitive impairment in terms of attention, visual-spatial memory, and the ability to perform.<sup>12</sup>

At present, various approaches, such as (Mini-Mental State Examination, MMSE) and (Montreal Cognitive Assessment, MoCA), are widely used in clinical practice. However, these scales are less sensitive to mild changes in the cognitive function. Negative results could be obtained if only a simple MMSE scale is used to evaluate the cognitive function of patients with migraine.

The relationship between migraine and cognitive function has been investigated in cross-sectional studies. The results are inconsistent. Several researchers believe that migraine does not lead to decreased cognitive function. Other researchers believe that the cognitive function of migraine patients is worse than that of healthy controls. Given the nature of these cross-sectional studies, they only focused on one point in time and disregarded the

difference between cognitive function decline in patients with migraine and that in healthy people as time progresses.

In Kalaydjian's research, the scores of 50-year-old patients with migraine with aura were significantly lower than those of the control group.<sup>13</sup> As age increased, the cognitive function of patients with migraine decreased more than that of the healthy group. In addition, no significant difference in cognitive function was observed between the 50-year-old and healthy control groups. Another study that assessed the cognitive function of patients with migraine by using a cognitive scale found no substantial effect on the cognitive function of patients with migraine.<sup>14</sup>

Compared with the control group, patients with migraine showed no significant difference in cognitive function. This result was obtained through cognitive scales, such as MMSE, digital symbol conversion test, connection test, verbal memory test, Benton visual retention test, verbal fluency test, finger tapping test, and face recognition test (an overall cognitive function evaluation method, similar to the simple mental state test).<sup>15,16</sup>

#### **MIGRAINE AND RESTING-STATE FUNCTIONAL MRI**

The rapid development of functional MRI (fMRI) enhanced our understanding of the relationship between brain function and different brain regions. fMRI is sensitive to brain metabolism and has a high spatial resolution; it determines neuron activity by measuring the change in the blood oxygen-dependent level signal.

Ideally, in the resting state, many brain regions perform spontaneous neuronal function activities, and differences in the space functional network are formed. In addition, the dynamic coordination of these brain functional networks may be closely related to cognitive and executive functions.<sup>17</sup>

#### ***A number of brain function networks exist as follows***

##### ***Central executive network (CEN)***

This includes the dorsal lateral prefrontal and parietal regions. It can guide senior cognitive processes and external attention-dependent secondary tasks.

##### ***Default mode network (DMN)***

It includes the medial prefrontal cortex, posterior cingulate cortex, and the anterior lobe of the wedge. This network requires basic cognitive support to complete inner spiritual exploration requirements, such as self-instruction, internal control, and episodic memory encoding.

### *Saliency network (SN)*

This network includes edge systems and is responsible for the integration of various sensory information in the brain from top-down information processing.

Recurrent pain attacks may affect the central executive function of network connectivity, thereby affecting the patient's cognitive function. A previous study compared resting-state fMRI (rs-fMRI) of a migraine group and found that the functional connectivity between the CEN regions of the group was enhanced.<sup>18</sup> Tessitore's study showed that in patients with migraine without aura, the functional connectivity between the frontal and temporal regions of DMN decreased.

The study also found a reduction in the activation of the right frontal gyrus and dorsal anterior cingulate gyrus in patients with migraine with aura.<sup>19</sup> No correlation was observed between the changes in functional connectivity in rs-fMRI and the brain structure and clinical or neuropsychological in patients with migraine.<sup>20</sup> These findings suggest that functional changes may precede structural abnormalities and may function as a barrier to the implementation of daily life activities with higher executive function. Therefore, the relationship between cognitive function and brain imaging findings in migraine patients still need to be studied through numerous experiments.

### **MIGRAINE AND EVENT-RELATED POTENTIAL**

Event-related potentials (ERP) are the responses of the brain to the stimulation of information. They reflect the brain's neural electrophysiological changes in the cognitive process and possess a high time resolution. ERPs are divided into exogenous (the human brain stimulates the production of the early composition and the physical characteristics of the stimulus) and endogenous (related to people's perception and cognitive psychological processing, such as attention, memory, and intelligence) components.<sup>21</sup> ERP studies have confirmed the presence of an abnormal visual cortical function in patients with headache, and this abnormal function varies among different types of headaches.

In addition, cognitive psychology exerts a significant effect on early ERP.<sup>22</sup> Meta-analysis shows that cognitive impairment and amplitude decrease in patients with P3 latency. P3 latency can be used as a sensitive index of early cognitive decline or mild cognitive dysfunction in patients with disease progression.<sup>23</sup> ERP can be used to evaluate the information transfer and cognitive function of the visual cortex in patients with migraine. Clinical studies suggest that a small N270 amplitude is associated with serious symptoms of anxiety and depression. N270 is thought to be an index of cognitive function in different domains, including attention and memory.<sup>24</sup> Therefore, N270 is suitable for evaluating the cognitive function of migraine. The temporal resolution of ERP and the

characteristics of brain activity can be used to study the change in the cognitive function of patients with migraine.

In Buodo G.'s research, cognitive processing was investigated interictally in 18 children with migraine without aura and 18 age-matched controls by measuring ERPs and reaction times during an acoustic oddball paradigm. The results showed that N100 amplitude evoked by frequent stimuli was significantly smaller in migraine patients compared with the controls.<sup>25</sup> In one of Andreatta M.'s studies, the migraine and control groups did not differ in their ratings of valence and arousal of the visual stimuli. However, in contrast to healthy controls, participants with migraine showed larger N170 amplitudes toward angry facial expressions compared with neutral expressions. Individuals with migraine may have an altered cortical activity linked to the processing of emotional information.<sup>26</sup>

Steppacher I.'s study showed that migraine patients had significantly more negative-going early ERP components from 100 ms to 180 ms to all picture categories over occipital regions as well as more positive-going late potentials over central regions compared with non-migraine patients. Thus, patients and controls did not differ in valence and arousal ratings for the international affective picture system. The results of their study are as follows. The facilitated processing may be related to the high cortical responsivity shown in many other ERP studies and may contribute to the recurring intense headache attacks<sup>27,28</sup>

The study of Kropp P. and Gerber WD. compared the habituation kinetics of contingent negative variation (CNV) among 12 migraineurs without aura and matched healthy controls. The most significant finding for the migraineurs was the lack of habituation of the early CNV component.

The present study indicates that instead of a generally increased cortical activity, delayed habituation is responsible for CNV abnormalities in migraine without aura. Between attacks, migraineurs not only experience cortical hyperexcitability but also a lack of cortical inhibition causing delayed habituation.<sup>29</sup> We can determine the change in habituation level over the migraine cycle, and the discourse of Coppola G. shows that the sensory cortices of migraineurs react excessively to repetitive but not to a small series of stimuli.<sup>30</sup> In conclusion, data against the concept of lack of habituation are considered a neurophysiological hallmark in migraine.<sup>28-31</sup>

Most studies have suggested that high and adaptive disturbance of episodic cortical excitability may further affect the cognitive function. A particular study concluded that migraineurs exhibit abnormal implicit evaluative processing of visual stimuli. The researchers asked two groups of participants and non-migraine

controls to view a set of unfamiliar commercial logos in the context of a target identification task as the brain electrical responses to these objects.

The migraineurs lacked a bias for disliked logos found in the control subjects as measured via a late positive potential (LPP) ERP component.<sup>32</sup> In the control subjects, the pain rating changed, suggesting a higher pain intensity; meanwhile, the basal hyperalgesia remained unmodified in the migraine patients. The N1 and N2 amplitudes changed coherently with the stimulus cue in the controls, whereas an opposite paradoxical increase in decreasing condition emerged in the migraine patients.<sup>33</sup> To sum up, migraine patients may exhibit gender-independent cognitive dysfunction, such as lack of attention, poor adaptability, and lack of ability to analyze the characteristics of things.

## CONCLUSION

Most of the recent studies on the cognitive function of patients with migraine were cross-sectional studies and lacked longitudinal and animal models. At present, research on the cognitive function of patients with migraine focuses on the cognitive domain, such as memory and attention, executive function, time perception, and analysis and problem solving ability. The cognitive function of patients with migraine may be affected by multiple factors, such as headache, age, type of headache, duration of headache, and gender.

Stroke and brain structural damage may increase the risk of cognitive impairment, and migraine patients may experience progressive brain structural damage associated with a high risk of cognitive dysfunction. A number of studies showed that cognitive impairment is not limited to patients with migraine, and the specificity of cognitive impairment in migraine patients requires further exploration. Although ERP may possess numerous advantages, it requires a variety of components and induced models, which lead to the study of the standard of evaluation of the cognitive function.

The test methods to evaluate the cognitive function of migraine patients in various studies are inconsistent and may result in inconsistent findings. Thus, research on the cognitive function of migraine patients requires further improvement. Future research should be conducted with a larger sample, a unified group, and a variety of cognitive assessment means to assess the cognitive function of patients with migraine. At the same time, we need to further explore the pathophysiological mechanisms of cognitive dysfunction in patients with migraine to provide a theoretical basis for the prevention and treatment of migraine.

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