Relationship Between Depression After Hemorrhagic Stroke and Auditory Event-Related Potentials in a Chinese Patient Group

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Purpose: Post-stroke depression (PSD) is the most common psychiatric sequelae of stroke. Numerous studies revealed that event-related potentials (ERP) can reflect depression severity to a certain extent, while there is almost no research on depression after hemorrhagic stroke. Therefore, we employed a prospective cross-sectional study to explore the relationship between ERP and depression after hemorrhagic stroke.

Methods: A total of 74 patients with intracranial hemorrhage were included in this study. Neurological deficits were evaluated using the National Institutes of Health Stroke Scale (NIHSS) on admission. Depression severity and cognitive impairment were measured using the 17-item Hamilton Depression Scale (HAMD-17) and the Chinese version of the Montreal Cognitive Assessment (MoCA) after two weeks of treatment. All patients were conducted auditory Oddball paradigm for event-related potential mismatch negativity (MMN) and P300.

Results: In total, 36 patients were diagnosed with PSD at the two weeks of treatment, for a percentage of 48.6%. Depression severity of ICH patients correlated positively with both the latency of MMN (r = 0.376, P = 0.001) and P300 (r = 0.325, P = 0.005), and correlated negatively with both the amplitude of MMN (r=−0.385, P = 0.001) and P300 (r=−0.311, P = 0.007). Depression severity was negatively correlated with cognitive function after hemorrhagic stroke (r=−0.347, P = 0.002).

Conclusion: The latency and amplitude of MMN and P300 can well reflect the degree of depression after hemorrhagic stroke, which may help in the early diagnosis and effective treatment of PSD.

Keywords: post-stroke depression, hemorrhagic stroke, event-related potential, MMN, P300

Introduction

Post-stroke depression (PSD) is the most common psychiatric sequelae of stroke. Previous studies have indicated that PSD had a negative contribution to survival quality, neurological functional recovery and sociability recovery, which heavily burdens the healthcare system.1 In recent years, the medical model has shifted from a single biomedical model to a biopsychosocial model.2 Therefore, attention should not be paid merely to the recovery of physical function but also psychological rehabilitation.

In current clinical settings, the monitoring of PSD mainly relies on clinical interviews and self-reported symptom checklists.3 Due to cognitive impairment and physical weakness, most stroke patients experience difficulty concentrating on the time-consuming appraisal process, leading to inefficient assessments. Moreover, patients with ICH typically presented to Neurology Department because of their severe organic symptoms. Although PSD has been emphasized gradually, for neurologists with insufficient psychiatric knowledge and training, timely identification and management of depressive symptoms can still be challenging.4,5
Numerous clinical studies have identified possible risk factors associated with PSD. Frequently cited factors include age, gender, functional and cognitive impairment, lesion location, history of depression, stroke severity and social support. However, most clinical studies include completely or mainly ischemic stroke patients and very few studies have been reported on patients with hemorrhagic stroke. Previous studies have indicated that the prevalence of PSD in hemorrhagic stroke patients was significantly higher than that of ischemic stroke patients. Depressive symptoms consisting of anxiety, loss of interest, insomnia, and fatigue were more frequent in patients with hemorrhagic stroke. This makes early identification and treatment of these patients critical to maximizing rehabilitation.

Physiological indicators that can objectively reflect the psychological condition may contribute to the sensitivity of PSD diagnosis. Event-related potential (ERP), an electrophysiological measurement, can localize and monitor neuropsychological activity in real-time to offer clinicians rich diagnostic information. Of these ERP components, mismatch negativity (MMN) and P300 may be the most suitable biomarkers for PSD, as they have already been wildly explored in poststroke cognitive impairment (PSCI), depression after ischemic stroke, and major depressive disorder (MDD). Numerous studies proved that MMN and P300 are promising biomarkers in these research areas and exhibit high potential application value. Yet the clinical application value of these ERP components in depression after hemorrhagic is still far from clear.

Therefore, we employed a prospective cross-sectional study to verify whether MMN and P300 can be used as specific indicators and to explore the potential factors related to depression after hemorrhagic stroke. Patients with first-ever intracranial hemorrhage (ICH) were recruited to undergo a detailed clinical examination and a battery of standardized neuropsychiatric scales, psychometric, and event-related potential tests. We hypothesize that the severity of depression can be indicated by the amplitude and/or latency of MMN and P300.

Materials and Methods
Patients with first-ever ICH hospitalized in the Neurosurgery Department of the Third Hospital of Mianyang between October 2020 and October 2021 were consecutively screened for our study. The inclusion criteria were as follows: (1) age between 40 and 70 years; (2) onset of ICH within 3 days; (3) stroke was confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) upon admission; and (4) received conservative treatment. The exclusion criteria included the following: (1) history of any central nervous system disease such as dementia, tumor or epilepsy; (2) a previous history of psychiatric disorders, such as depression; (3) severe aphasia, deaf or impaired consciousness that led to the failure of the assessment; (4) patients with a severe acute infection or severe somatic conditions; and (5) left-hander. The study protocol was approved by the Medical Ethics Committee of the Third Hospital of Mianyang. This study was carried out in accordance with the principles of the Declaration of Helsinki. All patients or their relatives signed written informed consent.

Baseline Information Collection
Demographic characteristics (age, sex, education level) and vascular risk factors (hypertension, diabetes mellitus, coronary artery disease, smoking and alcohol consumption) were recorded through a structured interview. All clinical data were collected by trained personnel. Cranial CT or MRI was performed on patients within 24 hours after admission. The hemorrhage site and hematoma volume were recorded according to the results of the CT or MRI images.

Treatment Methods
Nursing care and conservative treatment were carried out according to the Chinese guidelines for diagnosis and treatment of intracerebral hemorrhage (2019). The critical treatment measures include monitoring the patient’s vital signs, reducing intracranial pressure, stabilizing blood pressure maintaining the patient’s water, electrolyte and acid-base balance, preventing stress ulcers, preventing infection and neurotrophic therapy.
**Assessment**

In our study, stroke severity was assessed by experienced neurosurgeons using the National Institutes of Health Stroke Scale (NIHSS) upon admission. The NIHSS is often used to assess neurological deficits in patients and the higher the NIHSS score, the worse the neurological deficits.\(^\text{17}\)

When patients were in a stable clinical state (Patients can basically carry out daily activities but are accompanied by mild symptoms and signs, usually about two weeks after onset.),\(^\text{18}\) cognitive function and depression severity were assessed by two specially trained and qualified psychiatric physicians using the Chinese version of the Montreal Cognitive Assessment (www.mocatest.org, Full section) and the 17-item Hamilton Depression Scale,\(^\text{19}\) respectively. The Montreal Cognitive Assessment Scale (MoCA) is extensively used as an assessment instrument for cognitive dysfunction, and a score below 26 was considered cognitive impairment. The 17-item Hamilton Depression Scale (HAMD-17) is a multi-item scale wildly used by frontline medical staff to provide relevant information about depression, with higher scores signifying more severe depression. A HAMD-17 score >7 indicated depression according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria.\(^\text{20}\) Many scientific researchers have conducted similar investigations and shown that the construct validity and internal consistency of these scales are excellent.\(^\text{21,22}\)

**Measurement of ERP**

ERP recordings were taken by a trained and qualified electrophysiologist using an evoked potential recorder (MEB9200K, NIHON KOHDEN CORP). According to the International 10–20 EEG System, the recording electrode was placed at CZ point, the reference electrodes were placed at both mastoids, and the ground electrode was placed at FPz point (Figure 1). The impedance between electrodes and scalp was less than 5 kΩ. The classical auditory Oddball

![Figure 1](https://example.com/figure1.png)  
**Figure 1** Electrode placement. This figure is a visual representation of the electrode placement used according to the 10–20 system of electrode placement.
paradigm consisted of target stimulus and standard stimulus. The standard stimulus was a pure tone of 60 dB at 1000 Hz, with a probability of 80%, and the target stimulus was a pure tone of 80 dB at 2000 Hz, with a probability of 20%. ERP testing was conducted in two rounds. In the first round, patients were not required to respond to target stimulus and standard stimulus. The MMN was derived by subtracting non-target stimulation from target stimulation and superimposed 40 times. In the second round, patients were requested to respond to the target stimulus with a button press to obtain P300, superimposed 30 times. The confirmation of principal components and index values are referred to the maximum wave in the internationally recognized time window. Test indicators mainly include latency (straight-line distance from the start of stimulation to the horizontal axis of the maximum amplitude point of each component) and amplitude (vertical distance from the baseline to wave peak).

Statistical Analysis
We used SPSS 25.0 software version to analyze clinical variables, neuropsychological assessments and ERP data of all patients. The results of the categorical variables are shown as percentages. Continuous variables are expressed as the mean ± standard deviation (SD). A one-sample Kolmogorov–Smirnov Test was used to test data for normality. Analysis of variance (ANOVA) was used for comparisons between groups. To explore the relationship among different evaluations and the influences of different factors on the results, if the data is normal distribution, Pearson correlation analysis is used; if not, Spearman correlation analysis is used. P < 0.05 was considered to be statistically significant in all tests.

Results
A total of 83 stroke patients were included in our study (The trial flow diagram is presented in Figure 2). Patients with a history of depression (n = 2), consciousness disorder (n = 6) and left-handed (n = 1) were excluded. Ultimately, data on 74 patients [mean age, 59.2±9.6 years; 32 females (43.2%); high school or above, 28 (37.8%); NIHSS score, 10.7±5.5] with first-ever ICH were analyzed. Thirty-two (43.2%) patients scored lower than 26 on the MoCA scale, and thirty-six (48.6%) patients scored higher than 7 on the HAMD scale. Other baseline characteristics are presented in Table 1.

Figure 2 Study flow diagram.
Abbreviations: ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment (Chinese Version); HAMD-17, Hamilton Depression Scale (17-item); ERP, event-related potential.
Correlation analysis across different assessments are presented in Table 2. Our data showed that depression severity of ICH patients was associated with MMN and P300. Specifically, patients’ HAMD scores were positively correlated with the latency of MMN (r = 0.325, P < 0.05) and P300 (r = 0.376, P < 0.05), and also negatively correlated with the amplitude of MMN (r = −0.311, P < 0.05) and P300 (r = −0.385, P < 0.05). Our data also revealed that the depression severity was negatively correlated with cognitive function (MoCA score) (r = −0.347, P < 0.05), but not with NIHSS scores and hematoma volume.

Statistical comparisons between groups by ANOVA found depression severity was not associated with gender, education level, vascular risk factors (hypertension, diabetes mellitus, coronary artery disease, smoking, alcohol consumption) and hematoma side. The specific results are shown in Table 3.

Table 1 Baseline Characteristics of Patients with ICH

| Variables            | Patients with ICH, n = 74 |
|----------------------|---------------------------|
| n (%)                |                           |
| Female               | 32 (43.2)                 |
| High school or above | 28 (37.8)                 |
| Hypertension         | 58 (78.4)                 |
| Diabetes             | 3 (4)                     |
| Hyperlipidemia       | 14 (18.9)                 |
| Ever smoked tobacco  | 29 (39.2)                 |
| Ever drank alcohol   | 20 (27.0)                 |
| Cardiovascular disease| 4 (5.4)                  |
| Left side            | 44 (62.9)                 |
| x±s                  |                           |
| Hematoma volume (mL) | 14.7±7.2                  |
| NIHSS score on admission | 10.7±5.5               |
| MoCA score at 14 ± 2 days | 23.3±5.7            |
| HAMD-17 score at 14 ± 2 days | 9.7±5.5               |
| MMN latency (ms)    | 234.6±30.8                |
| MMN amplitude (μV)  | 11.8±10.8                 |
| P300 latency (ms)   | 400.9±37.1                |
| P300 amplitude (μV) | 11.1±10.9                 |

Abbreviations: ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment Scale (Chinese Version); HAMD-17, Hamilton Depression Scale (17-item); MMN, mismatch negativity.

Table 2 Correlation Analysis Between Clinical Features and HAMD

| Variables            | r   | P value |
|----------------------|-----|---------|
| Age                  | −0.145 | 0.217 |
| Hematoma volume      | 0.195  | 0.095  |
| NIHSS score on admission | 0.218  | 0.062  |
| MMN Latency          | 0.376  | 0.001  |
| MMN Amplitude        | −0.385 | 0.001  |
| P300 P300 Latency    | 0.325  | 0.005  |
| P300 Amplitude       | −0.311 | 0.007  |
| MoCA score at 14 ± 2 days | −0.347 | 0.002  |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment Scale (Chinese Version); MMN, mismatch negativity.
Discussion
As far as we are aware, this is the first study to explore the changes and characteristics of MMN and P300 in depressive patients with hemorrhagic stroke in China.

The mismatch negativity (MMN) is a crucial component of event-related potentials, mainly distributed in the forehead and central brain region, appearing in 100–250ms after deviant stimulus. The MMN reflects automatic identification of standard stimulus and biased stimulus, suggesting the automatic classification processing process of novel stimulus information. MMN reflects the pre-attentive processing and can be recorded even under passive attention condition. Going further, MMN manifests the autonomous capacity of brain auditory cortex. The auditory P300 is a late positive waveform first reported by Sutton in 1965, occurring at the latency of 300 ms after a specific stimulus, commonly used as a sensitive indicator to access early change in cognitive functioning. P300 is related to contextual updates and subsequent memory storage, providing cognitive process information including memory, attention, and mental processing speed.

The data indicated that MMN and P300 could well reflect the depression severity in our ICH patients. Take one step further, the more serious the depression, the longer the latency and lower the amplitude of MMN and P300. Certain studies have shown that depressed stroke patients exhibited prolonged latency and reduced amplitude of the MMN and P300 components compared to healthy individuals. One recent research has also revealed that the latency of these ERP components is longer in the PSD group compared with the pure depression group; meanwhile, amplitude showed the same tendency. These findings are in line with our data.

Although the pathogenesis of PSD has not been fully clarified, the significance and importance of some pathological mechanisms is beyond dispute. Hemorrhagic stroke can activate several signaling pathways, including oxidation, inflammation, autophagy and apoptosis, leading to the imbalance of multiple hormones, proinflammatory cytokines, neurotransmitters and neurotrophins, which would, in turn, promote depression occurrence. ERP is actually a result of neurochemical activities, which are directly or indirectly regulated by central neurochemicals. Numerous studies on ERP in psychopharmacology have verified the content and activity of central neurochemicals can induce alterations in ERP components.

ERP technology provides excellent time resolution, allowing detailed exploration of cognitive processes; even transient changes in brain activation can be captured. Moreover, ERP also enables the identification of relevant brain

Table 3 Analysis of Variance Between Clinical Characteristics and HAMD

| Variables             | HAMD-17 Score (x±s) | F     | P value |
|-----------------------|---------------------|-------|---------|
| Sex                   |                     |       |         |
| Male                  | 9.83±5.07           | 0.094 | 0.760   |
| Female                | 9.44±6.02           |       |         |
| Education level       |                     |       |         |
| High school or above  | 9.68±4.86           | 0.000 | 0.984   |
| Below high school     | 9.65±5.85           |       |         |
| Current smoking       |                     |       |         |
| Yes                   | 11.07±4.73          | 3.257 | 0.075   |
| No                    | 8.76±5.76           |       |         |
| Alcohol consumption   |                     |       |         |
| Yes                   | 10.90±5.35          | 1.414 | 0.238   |
| No                    | 9.20±5.49           |       |         |
| Hypertension          |                     |       |         |
| Yes                   | 9.26±5.54           | 1.472 | 0.229   |
| No                    | 11.13±5.08          |       |         |
| Diabetes              |                     |       |         |
| Yes                   | 6.67±5.51           | 0.938 | 0.336   |
| No                    | 9.79±5.47           |       |         |
| Hyperlipidemia        |                     |       |         |
| Yes                   | 11.14±5.49          | 1.272 | 0.263   |
| No                    | 9.32±5.45           |       |         |
| Cardiovascular disease|                     |       |         |
| Yes                   | 10.00±6.68          | 0.016 | 0.900   |
| No                    | 9.64±5.45           |       |         |
| Hematoma side         |                     |       |         |
| Left                  | 9.82±5.78           | 0.087 | 0.768   |
| Right                 | 9.43±5.05           |       |         |

Abbreviation: HAMD-17, Hamilton Depression Scale (17-item).
regions through source analysis.\textsuperscript{32} MMN and P300, as the classic endogenous components of event-related potentials, have been confirmed by a mass of research to be promising biomarkers of depression.\textsuperscript{14, 33} We assume that periodical evaluation of MMN and P300 will be conducive to reflecting depression severity and treatment response dynamically, thus guiding the personalized therapeutic schedule. Whereas further research is still needed to confirm our view.

Survivors with ICH have a very high prevalence of cognitive impairment; nearly 40\% developed dementia within five years.\textsuperscript{34, 35} Our results again demonstrated that patients with acute intracerebral hemorrhage are heavily risky to develop cognitive impairment. Possible reasons are ascribed as follows. First, most ICH events are acute manifestations of underlying cerebrovascular disease (CSVD), a progressive neurodegenerative disease of central nervous system.\textsuperscript{36} Previous studies have identified CSVD as one of the most robust risk factors for cognitive decline.\textsuperscript{37} Van et al\textsuperscript{38} found in a meta-analysis that depressive symptoms are closely associated with CSVD neuroimaging markers including white matter hyperintensity (WMH), lacunar infarction and cerebral microbleeds. Second, the stroke can damage functional areas of the brain, hinder the automatic processing of external information, and impair neurocognitive function.\textsuperscript{29} Nearly 84\% of ICH patients developed cognitive disorder in the acute stage.\textsuperscript{39} Relevant researches have pointed out that the decline of cognitive function and early onset of depression after ICH are the response to the acute mechanical destruction of brain network associated with cognitive and affective processes.\textsuperscript{34} Third, depression after hemorrhage stroke aggravates cognitive impairment.\textsuperscript{6} ICH, a severe disease with an extremely high disability and mortality rate, can cause tremendous psychological distress and lead to depression. Extensive studies have confirmed that depression may decline physical function in many aspects, leading to cognitive impairment. We also find that depression severity was negatively correlated with MoCA, suggesting that the more severe the PSD, the worse the cognitive function.

Researchers have been devoted to studying hematoma volume and side in PSD, but they still have not reached a consensus. We found no effect of hematoma volume and side on the results. Hadidi et al believe that PSD morbidity was independent of lesion site.\textsuperscript{41} Nys et al observed that PSD morbidity was only related to lesion size but not lesion location.\textsuperscript{42} Nevertheless, Shimoda et al found in a research that lesions in the left hemisphere increased depression incidence in stroke individuals, especially in the first few months after the onset of stroke.\textsuperscript{43} Instead, Wei et al found that right hemisphere lesions were strongly correlated with PSD in another meta-analysis.\textsuperscript{44} More studies are needed to determine whether hematoma volume and location affect PSD morbidity and elucidate its underlying mechanism.

Moreover, an association between PSD and gender, education level, vascular risk factors and NIHSS score were not found in the present study. We harbored this phenomenon might be attributed to the relatively small enrolled patient number and the exclusion of surgery patients.

Some limitations of this study should be considered. First, we merely conducted a single-center cross-sectional study. Also, only mild cases of patients presenting at a tertiary medical institution were enrolled in our study; this undoubtedly limits our findings’ spectrum and transregional use. Future research should expand the sample size, conduct multicenter and longitudinal research, recruit more diverse groups of ICH survivors, and elaborate the characteristics of ERP in patients with intracerebral hemorrhage at different degrees and different course stages. Second, limited by sample size, ethnicity, demographic homogeneity, geographical regions, and multiple restrictions, we did not find the effects of gender, education and vascular risk factors on PSD. Third, we only assessed depression severity through the HAMD-17 scale but did not conduct structured clinical interviews to confirm PSD. Moreover, we only collected ERP data through surface electrodes because of experimental conditions, which failed to rule out the interference of skull on EEG signals, which may reduce the accuracy of our results. In our opinion, multimodality techniques containing sLORETA, functional magnetic resonance imaging, TMS-EEG and microelectrode technology should therefore combine to conduct a deeper look.

Nevertheless, our present study promotes the identification and precision treatment of PSD and will help improve patients’ clinical symptoms and quality of life.

**Conclusion**

In summary, our study provides valuable insight into the potential utility of MMN and P300 in the diagnosis of depression after hemorrhagic stroke; that is, patients with more severe depression tend to exhibit longer latency and
lower amplitude of event-related potential MMN and P300. MMN and P300 provide unique advantages in diagnosing and evaluating depression after hemorrhagic stroke, which may help precision guidance for clinical treatment schemes.

**Disclosure**

The authors report no conflicts of interest in this work.

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