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ORIGINAL ARTICLE

Association of cognitive impairment and mood disorder with event-related potential P300 in patients with cerebral small vessel diseases

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Abstract

OBJECTIVE: Cerebral small vessel diseases (CSVDs) are common causes of cognitive impairments and mood disorders. In recent years, event-related potential P300 has received increasing attention as a biomarker of cognitive impairments or mood disorders. Previous studies on P300 mainly focused on anxiety, depression or cognitive impairments, and few results have been reported on P300 in CSVD patients. The present study aimed to explore the relationship between neuropsychological test scores and P300 in patients with CSVDs.

METHODS: The clinical data of 52 patients with CSVDs admitted to the Neurology ward of the First Hospital of Jilin University from June 2016 to October 2017 were collected. All patients who met the inclusion criteria were assessed by both cognitive tests and mood scales within 1 week after enrollment, followed by measurement of P300. Accordingly, patients were assigned to the following four groups: cognitive impairment, non-cognitive impairment, mood disorder, and non-mood disorder.The amplitude and latency values of P300 were measured from the Pz, Fz, Fpz, C3, C4 and Cz electrode sites. In addition, correlations of P300 responses and neuropsychological test scores were analyzed.

RESULTS: Significant differences were found in the P300 latency values between the cognitive impairment group and non-cognitive impairment group ($P<0.05$). P300 latency values were more significantly prolonged in the mood disorder group at the Fz, C3 and Cz electrode sites than in the non-mood disorder group. Positive correlations were found between Hamilton Depression Scale scores and C3, Fz and Cz latencies. Females tended to have a statistically higher risk of emotional impairment than did males ($p<0.05$).

CONCLUSION: P300 latency values can be used as a objective indicator of cognitive impairments and mood disorders in CSVD patients.

Abbreviations:
CSVD - Cerebral small vessel diseases
(ERPs) - Event-related potentials
MRI - Magnetic resonance imaging
MMSE - Mini Mental State Examination
MoCA - Montreal Cognitive Assessment
HAMD - Hamilton Depression Scale
HAMA - Hamilton Anxiety Scale
DSM–V - Diagnostic and Statistical Manual of Mental Disorder
CCMD-3 - Currently, the Chinese Classification and Diagnostic Criteria for Mental Disorder Version 3

INTRODUCTION

Cerebral small vessel diseases (CSVDs) are microvascular diseases involving cerebral white and gray matter such as lacunar infarcts, white matter lesions, and cerebral microbleeds. CSVDs represent a group of pathological processes with multifarious etiology and pathogeneses that involve the small vessels, including arterioles, venues, and capillaries of the brain (Pantoni 2010; Schmidtke & Hüll 2005). CSVDs are responsible for 20%–30% of cases of ischemic stroke as well as a considerable proportion of cases of cerebral hemorrhages and encephalopathy (Zhang *et al.* 2010). CSVDs gradually lead to decline of cognition, vascular dementia, and mood depression and often result in great social and economic burdens (Zhang *et al.* 2010).The pathogenesis of cognitive impairments and mood disorders within CSVD patients may involve disruption of the cortico-, striatal-, pallidal- and thalamic-cortical pathways, which may lead to the death of 5-hydroxytryptamin– and norepinephrine-expressing neurons and disruption of relevant pathways (Loubinoux *et al.* 2012).

Event-related potentials (ERPs) represent the activities of neurons that are synchronously activated, and P300 is the one of the most investigated components of ERPs. Basically, a large positive wave occurring approximately 300 ms after the target stimuli (Sutton *et al.* 1965) is characteristic of P300, which reflects cognitive processes during complex memory tasks and is related to focused attention, working memory, signal detection, and decision-making processes (Mecklinger *et al.* 1992; Johnson & Donchin, 1978). Most studies reported that the latency period of P300 is prolonged and the amplitude of P300 is decreased in patients with cognitive impairments and/or mood disorders (Kiiski *et al.* 2012; Dubovik *et al.* 2013; Zhang *et al.* 2013).

In the present study, we aimed to determine the dynamic changes caused by CSVDs in the brain by employing P300 responses in combination with neuropsychological tests in patients with cognitive impairments and/or mood disorders.

MATERIALS AND METHODS

Patients

CSVD patients hospitalized in the Neurology Department of the First Hospital of Jilin University from June 2016 to October 2017 were diagnosed according to the diagnostic standards for CSVDs. All patients provided written informed consent for participation, and the studywas approved by the appropriate ethics review board of the First Hospital of Jilin University. All participants underwent neurological examination and magnetic resonance imaging (MRI) prior to the study. The inclusion criteria for the study were: (1) age 18 years or older; (2) ability and willingness to give consent; and (3) meeting diagnostic standards for CSVDs (Pantoni, 2010; Schmidtke & Hüll, 2005). The exclusion criteria

Tab. 1. Clinical characteristics of patients in the cognitive impairment and non-cognitive impairment groups

	Cognitive impairment group (n=34)	Non-cognitive impairment group (n=18)	*P*
Age (years)	62.0±9.28	59.0±9.24	0.267
Male to female ratio	15:19	5:13	0.249
Educational attainment			
A	5	3	0.183
B	12	2	
C	12	7	
D	5	6	
History of hypertension (%)	61.80	55.60	0.664
History of diabetes (%)	38.20	38.90	0.963
Cholesterol (mmol/L)	4.36±1.25	4.79±1.23	0.262
Triglyceride (mmol/L)	1.87±0.83	1.77±0.68	0.687
LDL-C (mmol/L)	2.53±0.82	2.97±0.81	0.085
Glycated hemoglobin (%)	6.50±1.14	6.33±1.88	0.732

A: Primary school and below; B: junior high school; C: technical secondary school/senior high school; D: junior college/regular college course; LDL-C, low-density lipoprotein cholesterol.

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Tab. 2. Clinical characteristics of patients in the mood disorder and non-mood disorder groups

	Mood disorder group (n=14)	Non-mood disorder group (n=38)	*P*
Age (years)	63.6±9.76	60.0±9.04	0.213
Male to female ratio	5:9	27:11	0.020
Educational attainment			
A	3	5	0.851
B	4	10	
C	4	15	
D	3	8	
History of hypertension (%)	42.90	65.80	0.135
History of diabetes (%)	35.70	39.50	0.805
Cholesterol (mmol/L)	4.80±1.45	4.39±1.14	0.302
Triglyceride (mmol/L)	1.81±0.90	1.84±0.73	0.894
LDL-C (mmol/L)	2.81±0.93	2.64±0.81	0.534
Glycated hemoglobin (%)	6.15±0.77	6.51±1.71	0.519

A: Primary school and below; B: junior high school; C: technical secondary school/senior high school; D: junior college/regular college course; LDL-C, low-density lipoprotein cholesterol.

included: (1) lacunar infarction diameter >20 mm and major vascular stenosis; (2) inability to complete tests; (3) history of depression, anxiety or cognitive impairments; and (4) abnormal white matter signal caused by carbon monoxide poisoning or hypoglycemia. Clinical data from all patients were analyzed retrospectively, including age, gender, average educational attainment (A: primary school and below; B: junior high school; C: technical secondary school/senior high school; and D: junior college/regular college course), history of hypertension or diabetes, serum levels of cholesterol, triglyceride, low-density lipoprotein cholesterol, and glycated hemoglobin.

Neuropsychological assessment

A detailed neuropsychological test battery was applied to all participants by neuropsychologists. The following tests were administered: the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) to assess cognitive status (Hilal *et al.* 2017; Feng *et al.* 2012; Jeong *et al.* 2004) and the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) to assess mood disorders. At present, there is no unified specific standard for the diagnosis and evaluation of poststroke depression. Domestic and foreign scholars have basically adopted various diagnostic criteria, scales and parameters of functional depression. The

Tab. 3. P300 amplitude and latency values in the cognitive impairment group and non-cognitive impairment group

Electrode site	Cognitive impairment group (n=34)	Non-cognitive impairment group (n=18)	*P*
Pz latency (ms)	405.9±40.8	355.7±32.0	0.000
Fz latency (ms)	400.8±35.4	359.2±31.0	0.000
Fpz latency (ms)	388.1±51.8	348.1±28.5	0.006
C3 latency (ms)	400.8±35.8	352.4±28.5	0.000
C4 latency (ms)	405.6±36.4	357.0±32.2	0.000
Cz latency (ms)	402.3±36.0	353.7±29.1	0.000
Pz amplitude (μv)	8.68±7.10	7.26±4.33	0.442
Fz amplitude (μv)	8.81±7.53	8.77±6.18	0.983
Fpz amplitude (μv)	8.36±7.26	11.72±12.90	0.234
C3 amplitude (μv)	7.91±6.88	7.57±5.26	0.856
C4 amplitude (μv)	7.78±6.90	6.75±4.19	0.566
Cz amplitude (μv)	8.84±7.34	6.89±3.78	0.298

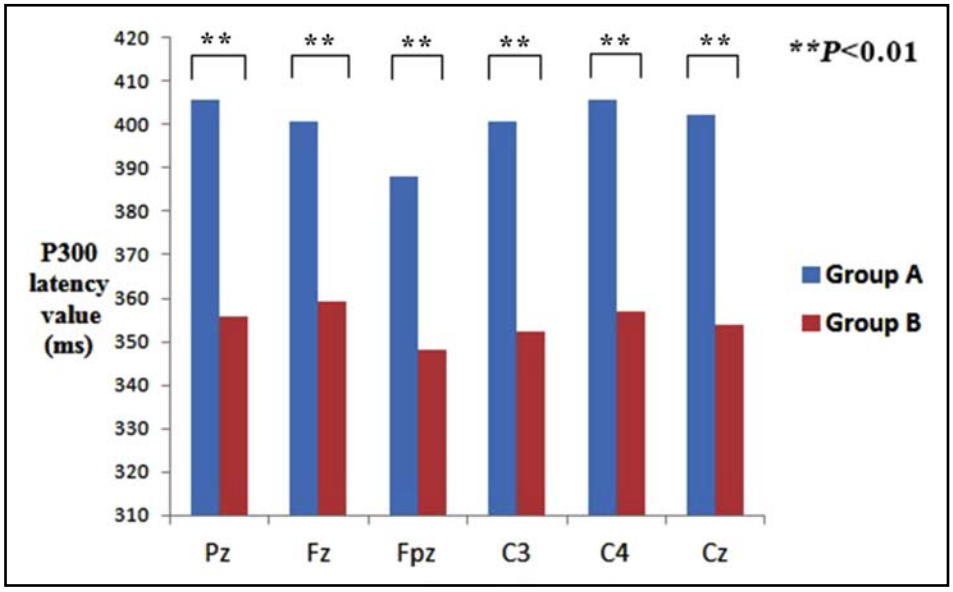

Fig. 1. P300 latency values in the cognitive impairment group and non-cognitive impairment group
Group A: cognitive impairment group; Group B: non-cognitive impairment group. The P300 latency values of the cognitive impairment group were prolonged compared with those of the non-cognitive impairment group over the electrode sites Pz, Fz, Fpz, C3, C4 and Cz.

diagnostic criteria used worldwide are the Diagnostic and Statistical Manual of Mental Disorder (DSM–V) (American Psychiatric Association, 2013). Currently, the Chinese Classification and Diagnostic Criteria for Mental Disorder Version 3 (CCMD-3) has been adopted in China. Regarding the first-line assessments of poststroke depression, the diagnostic test used most commonly is the HAMD. In the present study, patients with a score <27 (O'Bryant *et al.* 2008) on the MMSE and a score <26 (Nasreddine *et al.* 2005) on the MoCA were considered to be cognitively impaired. Patients with a score ≥7 on the HAMA and a score ≥8 on the HAMD were considered to be anxious and depressed, respectively. None of the enrolled patients had received any drug that either improves cognitive function or alleviates anxiety or depression.

Electrophysiological recordings

All P300 recordings were independently performed by a trained member from the research group in a sound-attenuated, isolated room. A classical oddball paradigm was used in the experiments. Regarding the P300, oddball task visual-evoked potentials were measured using a NeuroScan. The electrophysiologi-

Tab. 4. P300 amplitude and latency values in the mood disorder group and non-mood disorder group

Electrode site	Mood disorder group (n=14)	Non-mood disorder group (n=38)	*P*
Pz latency (ms)	404.2±34.1	381.4±47.0	0.117
Fz latency (ms)	406.9±24.6	378.3±41.0	0.018
Fpz latency (ms)	377.6±45.4	373.7±50.9	0.804
C3 latency (ms)	405.5±26.2	376.2±42.1	0.023
C4 latency (ms)	399.2±37.2	383.6±43.2	0.256
Cz latency (ms)	406.0±26.0	377.9±42.9	0.026
Pz amplitude (μv)	6.24±5.27	8.90±6.52	0.178
Fz amplitude (μv)	6.04±5.06	9.81±7.43	0.086
Fpz amplitude (μv)	7.01±4.50	10.44±10.80	0.257
C3 amplitude (μv)	6.06±4.36	8.43±6.84	0.234
C4 amplitude (μv)	5.41±4.03	8.17±6.56	0.148
Cz amplitude (μv)	7.09±5.98	8.57±6.53	0.464

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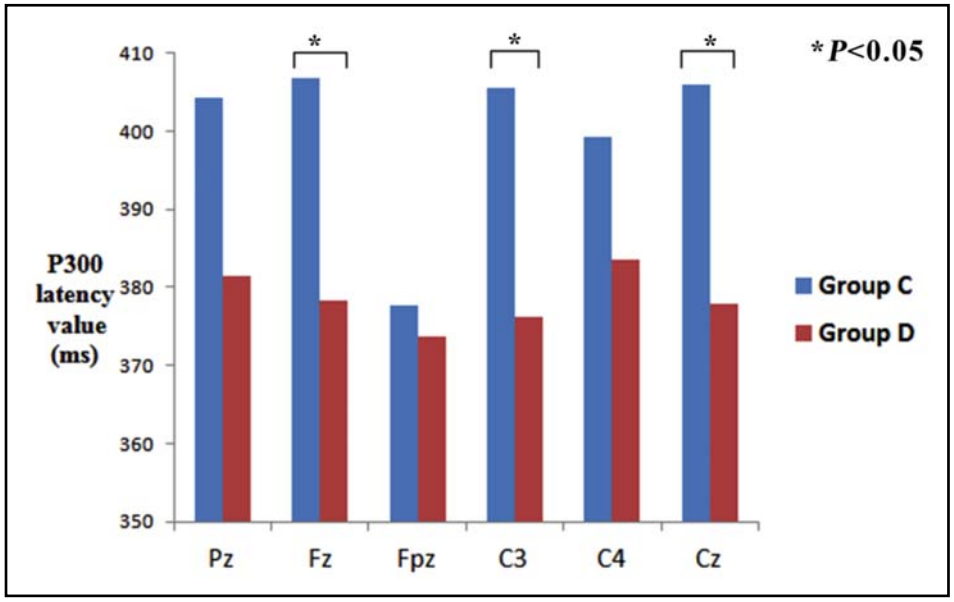

Fig. 2. P300 latency values in the mood disorder group and non-mood disorder group
Group C: mood disorder group; Group D: non-mood disorder group. The P300 latency values of the mood disorder group were prolonged compared with those of the non- mood disorder group over the electrode sites Fz, C3 and Cz.

cal activity was recorded from different positions: Fz (forehead midline), Cz (coronal midline), Pz (parietal midline), and Fpz (frontal pole). Impedances were less than 5 kΩ. In the oddball paradigm, we chose 2 for the target stimulus and 8 for the non-target stimulus. The P300 component was defined as the occurrence of the largest positive-going peak when responding to the deviant (rare) stimuli within a specific latency window (250–450 ms). Peak amplitude was measured relative to the prestimulus baseline (100 ms), and peak latency was measured from the time of stimulus onset (Hada *et al.* 2000).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Statistics (SPSS) version 17. The normally distributed measurement data are provided as mean ± standard deviation, and the means were compared using independent samples t test. Qualitative data were analyzed by chi-square (χ^2) test. The association of the neuropsychological test scores with values for P300 amplitude and latency among groups were analyzed based on partial correlation coefficients. Significance was accepted at a value of $p<0.05$ in all analyses.

Tab. 5. P300 amplitude and latency values in cognitive impairment with mood disorder group and cognitive impairment without mood disorder group

Electrode site	Cognitive impairment with mood disorder group (n=12)	Cognitive impairment without mood disorder group (n=22)	*P*
Pz latency (ms)	402.8±33.5	407.7±45.1	0.758
Fz latency (ms)	406.9±23.7	397.3±40.7	0.463
Fpz latency (ms)	387.8±40.1	388.3±58.7	0.981
C3 latency (ms)	407.1±23.7	397.6±40.7	0.484
C4 latency (ms)	394.7±38.5	411.6±34.7	0.224
Cz latency (ms)	407.0±24.2	399.7±41.4	0.581
Pz amplitude (μv)	6.32±5.60	9.96±7.61	0.155
Fz amplitude (μv)	6.19±5.41	10.24±8.23	0.136
Fpz amplitude (μv)	6.44±4.62	9.40±8.27	0.262
C3 amplitude (μv)	5.73±4.64	9.10±7.68	0.176
C4 amplitude (μv)	5.14±4.31	9.22±7.68	0.100
Cz amplitude (μv)	7.48±6.26	9.59±7.90	0.433

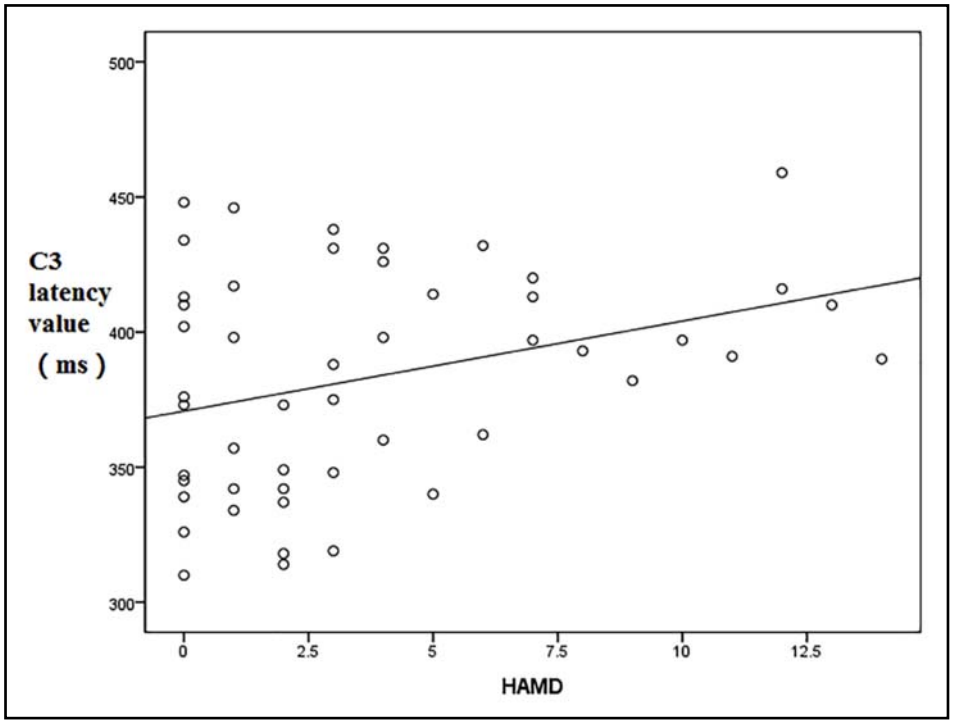

Fig. 3. Correlations between HAMD score and P300 latency value at the electrode site C3
According to the partial correlation analysis, a mild positive correlation was found between the HAMD score and C3 latency value (r=0.325, *P*=0.022).

RESULTS

Clinical data

This study enrolled a total of 52 patients with CSVDs, whose ages ranged from 43–77 years, and 38.5% were female. Concerning vascular risk factor distributions, of the 52 patients, 31 (59.6%) had hypertension, and 20 (38.5%) had diabetes. All patients who met the inclusion criteria were assessed by both cognitive tests and mood scales within 1 week after enrollment, followed by measurement of P300. Accordingly, patients were assigned to the following four groups: cognitive impairment group, non-cognitive impairment group, mood disorder group, and non-mood disorder group. Tables 1 and 2 show the clinical characteristics among the study groups. In this study, there were no significant differences in age, the male to female ratio, educational attainment, history of diabetes or hypertension, and levels of cholesterol, triglyceride, low-density lipoprotein cholesterol and glycated hemoglobin between the cognitive impairment and non-cognitive impairment groups (Table1). Only the ratio of males to females showed a significant difference between the mood disorder and non-mood disorder groups (5:9 vs 27:11, p=0.020; Table 2).

Comparison of P300 amplitude and latency between the cognitive impairment and non-cognitive impairment groups

The P300 latency values were found to differ significantly between the cognitive impairment group and the non-cognitive impairment group (p<0.01). According to the independent sample t-test, the P300 latency values of the cognitive impairment group were prolonged compared with those of the non-cognitive impairment group over the electrode sites Pz, Fz, Fpz, C3, C4 and Cz (Table 3, Figure 1). The P300 amplitude values did not differ between the two groups (P>0.05; Table 3).

Comparison of P300 amplitude and latency between the mood disorder and non-mood disorder groups

The P300 latency values of the mood disorder group were significantly prolonged compared to those of the non-mood disorder group over the electrode sites Fz, C3 and Cz (p<0.05; Table 4, Figure 2). The P300 amplitude values did not differ between the two groups (p>0.05; Table 4).

Comparison of P300 amplitude and latency between the cognitive impairment with mood disorder group and cognitive impairment without mood disorder group

The P300 latency and amplitude values of the cognitive impairment with mood disorder group and cognitive impairment without mood disorder group did not differ (p>0.05; Table 5).

Correlations between neuropsychological test scores and P300 amplitude and latency values

According to the partial correlation analysis, a mild positive correlation was found between HAMD score and C3, Fz and Cz latency values (r=0.325, p=0.022;

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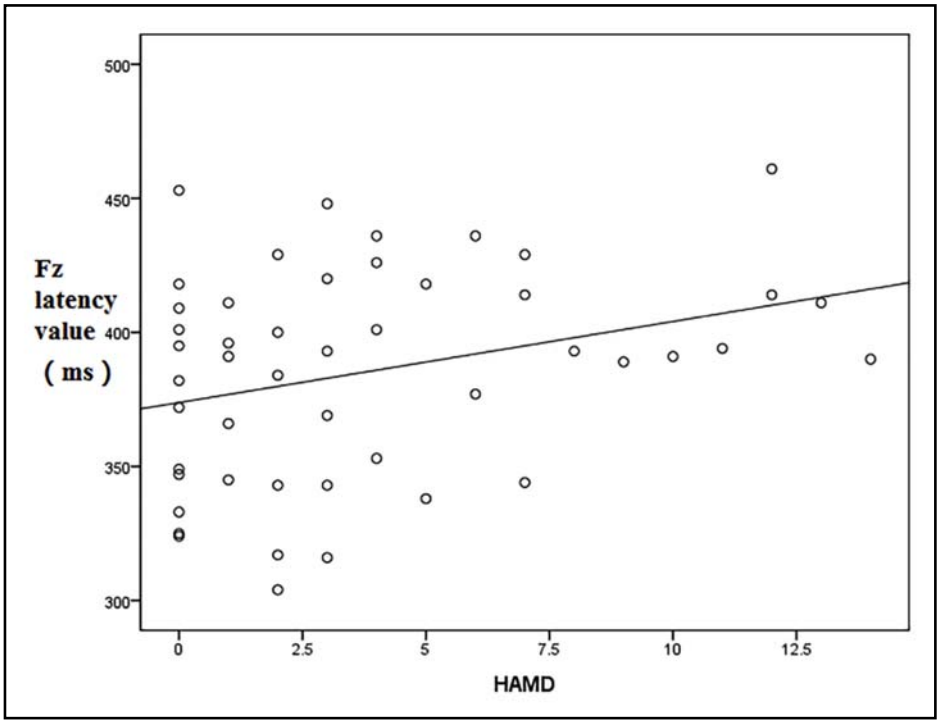

Fig. 4. Correlations between the HAMD score and P300 latency value at the electrode site Fz
According to the partial correlation analysis, a mild positive correlation was found between the HAMD score and Fzlatency value (r=0.304, *P*=0.036).

r=0.304, *p*=0.036; and r=0.300, *p*=0.036; respectively). The correlation analysis results are shown in Figures 3–5. In this study, no correlations were found between the visual P300 amplitude and latency values and the MMSE, MoCA, and HAMA scores.

DISCUSSION

P300 latency is known to reflect the information processing speed of individuals regarding stimulus detection and evaluation (Kutas *et al.* 1977). Amplitude is associated with attention, signal detection, and working memory (Ozmus *et al.* 2017). Amplitude cannot be parallel to the degree of cognitive dysfunction. Our studies indicated that the P300 values in the cognitive impairment group featured obvious prolongation of the latency in the Pz, Fz, Fpz, C3, C4 and Cz regions. This is similar to Fu XJ's findings (Fu *et al.* 2017). However, there were no significant differences in the amplitude values between patients with and without cognitive impairment. The results of the present study suggest that P300 latency values can be used as a objective indicator of cognitive impairment in CSVD patients. In the study, we also observed that there has been an extension of the P300 latency in a small number of patients of CSVD. However, the neuropsychological test of MMSE or MoCA was still in the normal range. This indicates that some patients' brain transmission function or the processing procedure has slowed down. These patients are more likely to gradually develop into cognitive impairment. Therefore, these patients should be closely followed up and given some treatments to improve brain function to prevent or slow the occurrence of cognitive impairment. However, whether P300 can be used for early identification of cognitive impairment of patients with CSVD still needs an extensive study.

Our results also showed that the incidence of mood disorders among CSVD patients was 26.9%, the incidence of depression was 23.1%, and the incidence of anxiety was 21.2%, similar to the results of previous studies (Castillo *et al.* 1993). Our findings also indicated that P300 values in mood disorder group feature an obvious prolongation of the latency values in the Fz, C3 and Cz regions, which is consistent with the results of Kalayam et al (1998). The results of the present study suggest that P300 latency values can be used as a objective indicator of mood disorder in CSVD patients.

The P300 latency and amplitude values were found to not differ between the cognitive impairment with mood disorder group and the cognitive impairment without mood disorder group. Our results also demonstrated that most patients who had cognitive impairment suffered from a mood disorder. It was thus presumed that the dysfunctional deficits of neurophysiological activity were suppressed in patients with mood disorders, given that the cortical excitability was decreased, and the cognitive capacity was reduced.

Consistently with Papaliagkas's study (Papaliagkas *et al.* 2008), MMSE and MoCA scores of CSVD did not correlate with P300 amplitude and latency values. It was speculated that the degree of cognitive impairment in the patients in this study was still mild and did

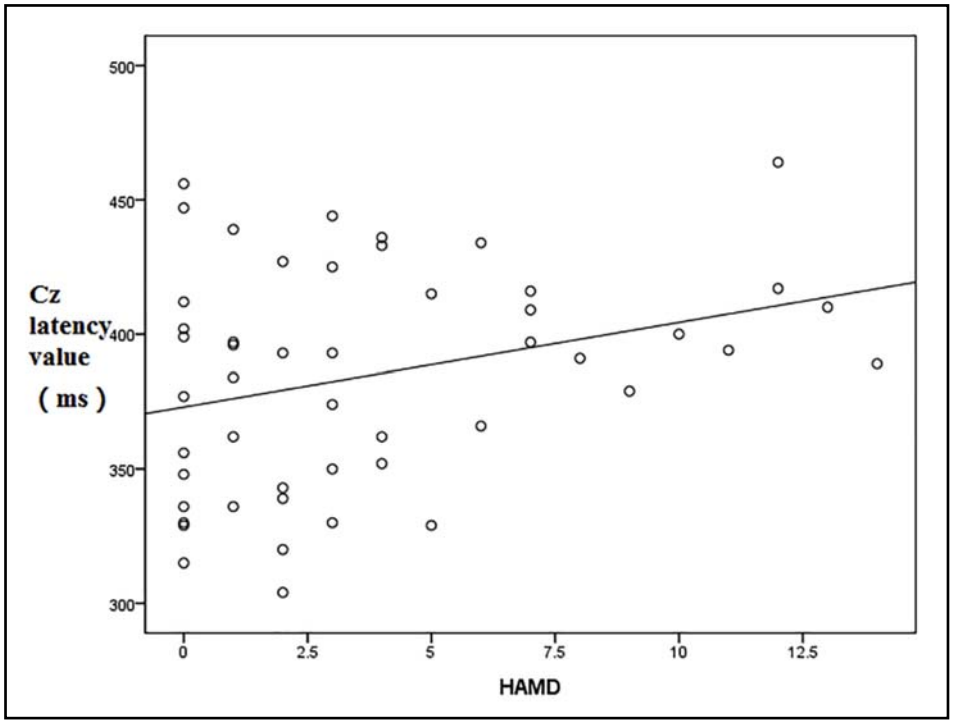

Fig. 5. Correlation between the HAMD score and P300 latency value at the electrode site Cz
According to the partial correlation analysis, a mild positive correlation was found between the HAMD score and Cz latency value (r=0.300, *P*=0.036).

not reach the severity of dementia. Even though some patients were very likely to gradually develop vascular dementia eventually, the degenerating brain still slowed the transmission and/or information processing.

Previous studies also found no significant correlation between the HAMD score and P300 values. In the present study, a mild positive correlation was observed between the HAMD score and values for C3, Fz and Cz latency, and this is likely because the majority of patients had mood disorders in addition to other symptoms such as cognitive dysfunctionin this study.

In the present study, the gender distribution of the mood disorder group was statistically different from that of the non-mood disorder group, which was consistent with the findings of previous studies (Cassidy *et al.* 2004). Of course, this result only represents the research in this region. It is generally believed that mood disorders are more likely to occur in female patients and may be related to distinctive hormone levels as well as neurotic tendencies among female patients. With regard to aging, female patients often experience disorder of neuroendocrine function, which represents a potential risk factor for anxiety and/or depression.

There are a number of potential limitations in our study. First, the number of enrolled patients was apparently insufficient, and hence, an expanded population is required for further analyses of the correlation between P300 amplitude/latency values and MMSE/MoCA scores. A second limitation is that CSVD subtypes were not considered in the present study. Such analysis may uncover more detailed information regarding the associations of P300 amplitude/latency values in cognitive impairments and mood disorders with CSVD subtypes, thereby potentially offering insights for the development of novel diagnostic approaches for recognizing the symptoms of CSVDs, especially in the early phase, in order to apply timely intervention and prevent disease progression.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

REFERENCES

1 American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorder. Fifth Edition. American Psychiatric Publishing. Available from: https://doi.org/10.1176/appi.books.9780890425596.
2 Cassidy E, O'Connor R, O'Keane V (2004). Prevalence of post-stroke depression in an Irish sample and its relationship with disability and outcome following inpatient rehabilitation. Disability and rehabilitation. **26**: 71–77.
3 Castillo CS, Starkstein SE, Fedoroff JP, Price TR, Robinson RG (1993). Generalized anxiety disorders after stroke. Journal of Nervous & Mental Disease. **181**: 100–6.

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4 Dubovik S, Bouzerda-Wahlen A, Nahum L, Gold G, Schnider A, Guggisberg AG (2013). Adaptive reorganization of cortical networks in Alzheimer's disease. Clinical neurophysiology. **124**: 35–43.
5 Feng L, Chong MS, Lim WS (2012). The modifed Mini-Mental state examination test: normative data for Singapore Chinese older adults and its performance in detecting early cognitive impairments. Singapore Med J. **53**: 458–62.
6 Fu XJ, Lu ZN, Wang Y, Huang LF, Wang X, Zhang H, et al (2017). A Clinical Research Study of Cognitive Dysfunction and Affective Impairment after Isolated Brainstem Stroke. Frontiers in Aging Neuroscience. **9**: 400.
7 Hada M, Porjesz B, Begleiter H, Polich J (2000). Auditory P3a assessment of male alcoholics. Biol Psychiatry. **48**: 276–86.
8 Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL (2017). Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. Journal of Neurology, Neurosurgery Psychiatry. **88**: 669–74.
9 Jeong SK, Cho KH, Kim JM (2004). The usefulness of the korean version of modified Mini-Mental state examination (K-mMMSE) for dementia screening in community dwelling elderly people. BMC Public Health. **4**: 31.
10 Johnson R, Donchin E (1978). On how P300 amplitude varies with the utility of the eliciting stimuli. Electroencephalography and Clinical Neurophysiology. **44**: 424–37.
11 Kalayam B, Alexopoulos GS, Kindermann S, Kakuma T, Brown GG, Young RC (1998). P300 latency in geriatric depression. American Journal of Psychiatry. **155**: 425–7.
12 Kiiski H, Reilly RB, Lonergan R, Lonerqan R, Kelly S, O'Brien MC, et al (2012). Only low frequency event-related EEG activity is compromised in multiple sclerosis: insights from an independent component clustering analysis. PLoS ONE. **7**: 1–12.
13 Kutas M, McCarthy G, Donchin E (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. Science. **197**: 792–5.
14 Loubinoux I, Kronenberg G, Endres M, Schumann-Bard P, Freret T, Filipkowski RK, et al (2012). Post-stroke depression: mechanisms, translation and therapy. Journal of cellular and molecular medicine. **16**: 1961–9.
15 Mecklinger A, Kramer AF, Straver DL (1992). Event related potentials and EEG components in a semantic memory search task. Psychophysiology. **29**: 104–19.
16 Nasreddine Z S , Phillips N A , Bédirian V, Charbonneau S, Whitehead, V, Collin I, et al (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. Journal of the American Geriatrics Society. **53**: 695–699.
17 O'Bryant SE, Humphreys JD, Smith GE, Ivnik RJ, Graff-Radford NR, Petersen RC, et al (2008). Detecting Dementia With the Mini-Mental State Examination in Highly Educated Individuals[J]. Archives of neurology. **65**: 963–967.
18 Ozmus G, Yerlikaya D, Gokceoglu A, Savas DDE, Cakmur R, Colakoglu BD, et al (2017). Demonstration of Early Cognitive Impairments in Parkinson's Disease with Visual P300 Responses. Archives of Neuropsychiatry. **54**: 21–27.
19 Pantoni L (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology. **9**: 689–701.
20 Papaliagkas V, Kimiskidis V, Tsolaki M, Anogianakis G (2008). Usefulness of event-related potentials in the assessment of mild cognitive impairment. BMC Neuroscience. **9**: 107.
21 Schmidtke K, Hüll M (2005). Cerebral small vessel disease: how does it progress? Journal of the Neurological Sciences. **229-230**: 13–20.
22 Sutton S, Braren M, Zubin J, John ER (1965). Evoked-potential correlates of stimulus uncertainty. Science. **150**: 1187–8.
23 Zhang AJ, Yu XJ, Wang M (2010). The clinical manifestations and pathophysiology of cerebral small vessel disease. Neuroscience bulletin. **26**: 257–64.
24 Zhang M, Chen M, Wang Q, Yun W, Zhang Z, Yin Q, et al (2013). Relationship between cerebral microbleeds and cognitive function in lacunar infarct. Journal of International Medical Research. **41**: 347–55.