Predictive power of abnormal electroencephalogram for post-cerebral infarction depression

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Abstract
Electroencephalography is a sensitive indicator for measuring brain condition, and can reflect early changes in brain function and severity of cerebral ischemia. However, it is not yet known whether electroencephalography can predict development of post-cerebral infarction depression. A total of 321 patients with ischemic stroke underwent electroencephalography and Hamilton Depression Rating Scale assessment to analyze the relationship between electroencephalography and post-cerebral infarction depression. Our results show that electroencephalograms of ischemic stroke patients with depression exhibit low-amplitude alpha activity and slow theta activity. In contrast, electroencephalograms of ischemic stroke patients without depression show fast beta activity and slow delta activity. These findings confirm that low-amplitude alpha activity and slow theta activity can be considered as independent predictors for post-cerebral infarction depression.

Key Words: nerve regeneration; cerebrovascular disease; brain organic mental disorders; stroke; ischemic stroke; post-cerebral-infarction depression; depression; electroencephalography; Hamilton Depression Rating Scale; neural regeneration
Introduction

Post-cerebral infarction depression (PCID) is the main form of post-stroke depression (PSD) and encompasses the majority of stroke. PCID is a common neuropsychiatric complication that affects the life quality of patients, and with symptoms involving consciousness and language, and mental retardation. The earliest study of PSD was in 1924 (Burvill et al., 1997). Burvill et al. (1997) performed experiments that found stroke patients were prone to behavioral and psychological disorders after brain injury. PSD was further confirmed as a persistent state in 1951, although the results were not widely noticed by medical academics. Folstein et al. (1977) performed clinical studies showing that PSD is a common complication of stroke patients, with an incidence rate of up to 45%. This attracted the attention of the medical profession, and PSD research became a ‘hot’ topic.

As a common psychiatric complication after ischemic stroke, PCID is a neurological disorder associated with depression. It refers to patients in a depressed state and includes a variety of neurological diseases or diseases. PCID symptoms include low mood and loss of interest, physical symptoms (such as sleep disorders, appetite disorders, and non-specific somatic symptoms), and psychological symptoms (such as anxiety, depression, mood, self-guilt, and self-reproach). Patients with a severe form of the illness even have tendencies of delusion and suicide. Therefore, detailed disease information cannot be obtained by clinicians, which is coupled to a lack of specific laboratory examinations and treatments for patients, as well as high rates of misdiagnosis and missed diagnosis within PCID patients (Shen, 2015). The prevalence of depression is up to 80% among cerebral infarction patients under conservative treatments (Li and Ma, 2015). Invasive treatment strategies may show some improvement for this unfavorable prognosis.

Related factors and mechanisms for PSD onset are not yet fully clear. It is generally believed that PSD is caused by interaction between biological, social, and psychological factors. PSD is an organic change in brain tissue involving the limbic-cerebral hemisphere system (specifically, prefrontal cortex, striatum, globus pallidus, and thalamus), and thereby affects regulation of circulatory dysfunction related to emotional disorders (Finnigan et al., 2004), accompanied by changes in states of consciousness. Studies have shown that cerebral blood flow is blocked for 30 seconds with cerebral infarction. Further, nerve cell membrane potential activity is abnormal, and the resulting changes can be observed by electroencephalography (EEG). Hence, EEG activity is viable for understanding changes in PSD pathogenesis, auxiliary diagnoses, and monitoring evaluation of its therapeutic effect, which support the theoretical foundation.

Changes in regional brain pathology function influenced by ischemic stroke can be analyzed via well-established, sensitive EEG. EEG is a low-cost, noninvasive imaging technique that can measure nerve electrophysiology in the brain with excellent temporal resolution. Moreover, EEG has been explored for prognosis in acute stroke for over 40 years (Kaste and Waltimo, 1976). There studies on whether further courses of depression can be predicted using EEG changes (Peltz et al., 2010; Assenza et al., 2013). Independent prediction of PCID is assessed by presence of abnormal EEG features, with the aim of early identification of depression and enabling interventional treatment strategies during a ‘window of opportunity’. Here, our study sought to identify predictive factors for PCID by analyzing abnormal EEG signals in patients.

Subjects and Methods

Subjects

In total, 321 cerebral infarction patients were selected from the Neurology Clinic of Shenzhen Second People’s Hospital in Guangdong Province of China from July 2015 to February 2016. Inclusion criteria were: patients in Guangdong Province of China who had brain imaging tests, either computerized tomography (CT) or magnetic resonance imaging (MRI), combined with diagnostic criteria for stroke that conform to the fourth National Cerebrovascular Disease Conference in 1995 (Chinese Society of Neuroscience and Chinese Neurosurgical Society, 1996), and who were consequently diagnosed with cerebral infarction. Patients had stroke onset within 7 days, with vital signs of stability and sanity, did not suffer from obvious speech disorders (including partial motor aphasia without sensory aphasia), and cooperated with examination. Exclusion criteria were: initial involvement of additional vascular territories; taking any sedatives; or a history of other mental illnesses, such as depression. Cerebral infarction patients were classified into two categories, irrespective of sex, for direct comparison: middle-aged < 60 years old and elderly > 60 years old (Additional file 1). Subjects were further divided into two subgroups: PCID group (score results ≥ 8 scores) and non-PCID group (score results < 8 scores) (Additional file 2), based on Hamilton Depression Rating Scale (HAMD) scale score (Assenza et al., 2013). Figure 1 shows a flow chart of the study. All subjects provided informed consent.

Data on demographics (sex and age), time after stroke, and frequency of stroke were collected from hospital electronic medical records. EEG examination within 7 days after onset is a standard procedure for incidence of cerebral infarction, and was generally performed in the hospital.

According to the formula for estimating sample size, \( n = \frac{400 \times (q/p)^2}{\text{error}^2} \), where \( p \) is the prevalence rate and \( q = 1 - p \). In this study, \( p = 72.6% \), with a resulting \( n = 156 \). The number of patients used for the study was 321, which is more than 156, and therefore meets the estimated sample size.

HAMD scale assessment

HAMD factors include anxiety, weight loss, cognitive disorders (e.g., guilt, suicide, and agitation), day and night changes, changes in job interest symptom retardation, sleep disturbances, and hopelessness. These factors accurately reflect a patient's psychopathology, and the target group's clinical symptoms. Classification of evaluation results: total score < 8 points is normal; total score 8–20 points may have depression; total score 20–35 points represents depression; total score > 35 points represents severe depression. The highest HAMD scale score is 133 points. Low HAMD scale scores
Table 1 Baseline characteristics and abnormal electroencephalogram

| Variables           | Non-PCID group (n = 88) | PCID group (n = 233) | P   |
|---------------------|-------------------------|----------------------|-----|
| Age (year, n%)      | 1.40±0.65               | 1.37±0.68            | 0.047|
| Middle-aged         | 42(47.7)                | 83(35.6)             |     |
| Elderly             | 46(52.3)                | 150(64.4)            |     |
| Gender (n%)         |                         |                      | 0.26|
| Male                | 65(73.9)                | 157(67.4)            |     |
| Female              | 23(26.1)                | 76(32.6)             |     |
| Frequency of strokes| 1.40±0.65               | 1.37±0.68            | 0.73|

Data are displayed as the mean ± SD unless indicated. Differences of continuous and categorical variables were separately evaluated by independent samples t-test and chi-square test. Stroke frequency: Incidence times of cerebral infarction before electroencephalography.

During sleeping, Reasonable EEG spectroscopy of 20–30 minutes was used in the sober and non-interference stages. EEG features were usually based on power ratios of alpha, beta, theta, and delta bands (Finnigan et al., 2004). Spectral analysis of EEG signals were performed by a certified EEG examiner (Li-jie Ren and Yan-qing Wang), who had understanding of stroke without knowledge of the clinical course.

**EEG analysis**

Raw EEG recording data from ischemic stroke patients were analyzed. The following parameters were considered: (1) involvement of occipital background frequencies to determine whether they are equal to, greater, or less than 8 Hz; (2) slowing activity influencing the entire hemisphere; (3) characteristic parameters within the spectrum (e.g., amplitude, activity, persistence, and reactivity of focal or lateralized slowing) (Ahmed, 1988); (4) slowing activity outside the ischemic lesion; and (5) regional attenuation without delta (RAWOD) (Schneider and Jordan, 2005).

**Statistical analysis**

Differences of continuous and categorical variables were separately evaluated by independent samples t-test and chi-square test. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by binary logistic analysis for abnormal EEG features in the PCID and non-PCID groups. The groups and models were unadjusted and adjusted for age, gender, and EEG recordings (frequency of strokes). All data were analyzed using IBM SPSS19.0 software (IBM, Armonk, NY, USA). Statistical significance was set at two-tailed P < 0.05.

**Results**

Baseline characteristics and abnormal EEG analysis in patients with or without depression

Baseline characteristics of 321 patients are shown in Table 1. The number of subjects was greater in the depression group than that in non-depression group. Stroke frequency before EEG was lower in the depression group than that in the non-depression group. The variables, middle-aged and elderly, were significantly associated with depression after cerebral infarction. However, they were not significantly associated with depression for age variables when estimated by
Table 2 Abnormal EEG characteristics

| EEG features | Depression No. | Prevalence (%) | P     | OR (95% CI)      | Adjusted OR (95% CI) |
|--------------|----------------|----------------|-------|------------------|---------------------|
| Alpha activity |                |                | 0.017 |                  |                     |
| Normal       | 75             | 32.2           | 1.00  | 1.00             |                     |
| Low-amplitude | 158            | 67.8           | 1.84  | (1.11–3.03)      | 1.85 (1.11–3.06)    |
| Beta activity |                |                | 0.189 |                  |                     |
| No           | 183            | 78.5           | 1.00  | 1.00             |                     |
| Yes          | 50             | 21.5           | 0.69  | (0.39–1.20)      | 0.70 (0.40–1.23)    |
| Theta activity |                |                | 0.033 |                  |                     |
| No           | 76             | 32.6           | 1.00  | 1.00             |                     |
| Yes          | 157            | 67.4           | 1.72  | (1.04–2.84)      | 1.76 (1.06–2.92)    |
| Delta activity |                |                | 0.383 |                  |                     |
| No           | 195            | 83.7           | 1.00  | 1.00             |                     |
| Yes          | 38             | 16.3           | 0.76  | (0.41–1.41)      | 0.75 (0.40–1.41)    |

EEG features are based on power ratios of alpha, beta, theta, and delta bands. Adjusted OR (95% CI) was adjusted for age and gender. EEG recording: time after stroke and frequency of strokes. ‘8–13 Hz; alpha volatility below 25 μV; 14–30 Hz; 4–7.5 Hz; 0.3–3.5 Hz. Incidence was analyzed by chi-square test. *P < 0.05. OR: Odds ratio; CI: confidence interval; EEG: electroencephalography.

95% CI in logistic regression models.

Analysis of abnormal EEG characteristics

Data for independent prediction of PCID, and OR (95% CI) by abnormal EEG features are shown in Table 2. Prevalence for low-amplitude alpha activity and slow theta activity were higher in the depression group than that in the non-depression group, whereas data for fast beta activity and delta activity were lower. Cerebral infarction patients suffered from depression predominant with low-amplitude alpha activity (adjusted OR 1.85 [1.11–3.06]) and slow theta activity (adjusted OR 1.76 [1.06–2.92]). Neither group was significantly associated with fast beta activity and slow delta activity.

Discussion

In our 321 cerebral infarction patients, EEG recordings can be considered independent predictors of clinical course. Similarly, EEG recordings provide useful information for identifying cerebral infarction patients who may develop depression. Our findings indicate that cerebral infarction patients predominantly experience depression with low-amplitude alpha activity and slow theta activity. In contrast, beta activity and slow delta activity were not significantly associated with development of depression in cerebral infarction patients. These results are in accordance with previous studies (Peltz et al., 2010; Assenza et al., 2013).

Detection of EEG is user-friendly, relatively simpler than imaging patterns, and can be quickly accessed. EEG is sensitive to disturbed neuronal functioning caused by energy depletion, such as cerebral infarction. EEG changes in cerebral infarction can be observed within minutes. Meanwhile, EEG can also measure developments of pyramidal neurons in response to decreased cerebral blood flow and hypoxia. There are relationships between reduced cerebral blood flow, degree of neuronal damage, and changes in EEG morphology (Faught, 1993; van Putten and Tavy, 2004). Serial EEG recordings have been investigated for their potential utility in predicting clinical course during recovery. Nerve cell function declines and relative amplitude of neural activity weakens in cerebral infarction patients with hypoperfusion, which results in low-amplitude alpha activity (Pollock and Schneider, 1990). Previous studies have found that slow theta activity is a predominant sign in PCID patients (Cillessen et al., 1994; Jordan, 2004). The 121 symptoms of major depressive disorder subjects indicate the appearance of theta activity and alpha activity in longer haul via QEEG (Deslandes et al., 2004; Leuchter et al., 2012).

Our results indicate that patients are regarded as having depression when EEG morphologies of low-amplitude alpha activity and slow theta activity appear. In our study, the presence of beta activity and slow delta activity after infarction suggested the patients were at low risk of depression. Continuous slow theta activity appears to be the most sensitive parameter in progression of depression by means of focal signs. Predominant low-amplitude alpha activity is a risk for PCID. Absence of slow activity and slight depression of alpha activity are excellent EEG predictive factors. Unfavorable predictor outcomes were low-alpha volatility activity and delta activity (Peltz et al., 2010; Assenza et al., 2013). We found that low-amplitude alpha activity together with continuous slow theta activity is predictors of PCID. Contradictory findings may be due to differences in living habits, for example, having a light diet and taking a break after lunch.

EGG, with an additional field, comes into the picture that it can predict the progress of depression following onset of stroke. This may be a progressive process in ischemic tissue, along with a possible reversible window for neuronal injury (Khodayari-Rostamabad et al., 2011). Whether neuronal injury leading to depression is reversible is not distinguishable in the clinic (Jordan, 2004). Even depression scales do not necessarily reflect depression course. EEG findings are relevant to good long-term prognosis, for example, absence of low-amplitude alpha activity and slow theta activity are considered predictive factors of a reversible state (Begić et al., 2011). Thus, for this indication, EEG might be included in future guidelines. Potential applications for PCID include early detection and follow-up courses, although diagnostic values must be established.
Our study is novel in identifying abnormal EEG characteristics as an independent risk factor for PCID in Chinese people of the Guangdong Province. The HAMD scale is used for depression diagnosis under normal conditions. It is assessed by a family member through recording medical history and observing clinical symptoms of the patient. The HAMD scale is relatively objective compared with other scales. Furthermore, rigorous quality control and face to face interviews are used by hospital employees for the HAMD scale. Consequently, HAMD score data are statistically significant in the study.

Subjects in our findings were chosen from the Shenzhen Second People’s Hospital of China. The sample size and representativeness might be limited, and all of those might influence the statistical results for HAMD scores. EEG signals were analyzed by certified examiners (instead of Matlab software) to acquire sampling rates, and performed in signal analysis, which might over- and underestimate the relationship. In addition, there are not any uniform international standards in use of Matlab software for EEG diagnosis. Observational bias might exist when depression is assessed by HAMD scale and clinical features. Hence, attention should be paid to explaining and comparing findings. Based on these findings, future research is needed to select different cerebrovascular disease types, adopt scales combined with the Self-Rating Depression Scale and HAMD, and use Matlab software for spectral analysis of EEG signals.

In summary, conventional EEG has been applied for cerebral infarction patients. Sole use of scales to diagnose depression might be susceptible to subjective assessment. EEG generated information may forecast depression onset after cerebral infarction and contribute to identifying intrusive treatment strategies within the window of probability. Therefore, the influence of depression may be minimized as well as permanent neuro- logical weaknesses decreased. Presence of low-amplitude alpha activity and slow theta activity are independent predictors of PCID. Intensive interventions should be targeted to reduce deaths due to depression in cerebral infarction patients.

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Author contributions: YPZ and FXW performed statistical analysis and wrote the paper. ZWZ and ZWW were responsible for data collection. YQW, DQZ and JL analyzed EEG signals. PL and JW gave the guidance of study design. All authors approved the final version of the paper.

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Additional files:

Additional file 1: Single sample test for Hamilton Depression Scale (HAMD) score.

Additional file 2: Logistic regression models analysis for age group.

References

Ahmed I (1988) Predictive value of the electroencephalogram in acute hemispheric lesions. Clin Electroencephalogr 19:205-209.

Assenza G, Zappasodi F, Pasqualetti P, Vernieri F, Tecchio F (2013) A contralesional EEG power increase mediated by interhemispheric disconnection provides negative prognosis in acute stroke. Restor Neurol Neurosci 31:177-188.

Begić D, Popović Knapić V, Grubišin J, Kosanović-Rajačić B, Filipić I, Telarović I, Jakovljević M (2011) Quantitative electroencephalography in schizophrenia and depression. Psychiatr Danub 23:355-362.

Burvill P, Johnson G, Jamrozik K, Anderson C, Stewart-Wynne E (1997) Risk factors for post-stroke depression. Int J Geriatr Psychiatry 12:219-226.

Chinese Society of Neuroscience and Chinese Neurosurgical Society (1996) Diagnosis of various cerebrovascular diseases. Zhonghua Shenjinkge Zazhi 29:379-380.

Cillesen JP, van Huffelen AC, Kappelle LJ, Algra A, van Gijn J (1994) Electroencephalography improves the prediction of functional outcome in the acute stage of cerebral ischemia. Stroke 25:1968-1972.

Deslandes A, Veiga H, Cagy M, Fiszman A, Piedade R, Ribeiro P (2004) Quantitative electroencephalography (qEEG) to discriminate primary-ary degenerative dementia from major depressive disorder (depression). Arq Neuropsiquiatr 62:44-50.

Faught E (1993) Current role of electroencephalography in cerebral ischemia. Stroke 24:609-612.

Finnigan SP, Rose SE, Walsh M, Griffin M, Janke AL, McMahan KL, Gillies R, Strudwick MW, Pettigrew CM, Semple J, Brown J, Brown P, Chalk JB (2004) Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI. Stroke 35:899-903.

Folstein MF, Folstein SE, McHugh PR (1975) “Mini-mental state”.” A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-198.

Graff-Radford NR, Bearinger SM, Shin YO, Scales CD, Thal LJ (1995) Quantitative EEG measures of injury and outcome in patients with head injury. Electroencephalogr Clin Neurophysiol 96:170-181.

Huang H, Zou J, Zhai F (2008) Quantitative EEG predicts outcome of patients with severe closed head injury. J Neurosurg Sci 52:131-137.

Kaste M, Walsimo O (1997) Prognosis of patients with middle cerebral artery occlusion. Stroke 7:482-485.

Khodayar-Rostamabad A, Reilly JP, Hasey GM, MacCrimmon D (2011) Using pre-treatment electroencephalography data to predict response to transcranial magnetic stimulation therapy for major depression. Conf Proc IEEE Eng Med Biol Soc 2011:6418-6421.

Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S (2012) Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One 7:e32508.

Li LJ, Ma X (2015) A Guide to the Prevention and Treatment of Depression in China (II). Beijing: Chinese Medical Multimedia Press Co., Ltd.

Peltz CB, Kim HL, Kawas CH (1990) Abnormal EEGs in cognitively and physically healthy oldest old: findings from the 90+ study. J Clin Neurophysiol 7:292-295.

Pollock VE, Schneider LS (1990) Quantitative, waking EEG research on depression. Biol Psychiatry 27:757-780.

Schneider AL, Jordan KG (2005) Regional attenuation without delta (RAWOD): a distinctive EEG pattern that can aid in the diagnosis and management of severe acute ischemic stroke. Am J Electroencephalogr Technol 45:102-117.

Shen JX (2015) The clinical significance of SEP and plasma serotonin in patients with post-stroke depression. Tianjin: Tianjin University.

Sheng LX (2015) The clinical significance of SEP and plasma serotonin in patients with post-stroke depression. Tianjin: Tianjin University.

Telarović I, Jakovljević M (2011) Quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. J Clin Neurophysiol 28:292-295.

van Putten MJ, Tavy DL (2004) Continuous quantitative EEG monitoring in hemispheric stroke patients using the brain symmetry index. Stroke 35:2489-2492.

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