Original Article

Correlation between Electroencephalogram Alterations and Frontal Cognitive Impairment in Esophageal Cancer Patients Complicated with Depression

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Abstract

Background: Some esophageal cancer patients complicated with depression exhibit cognitive impairments. Frontal electroencephalogram (EEG) may be used as a reliable biomarker for prefrontal-mediated cognitive functions. This study was to investigate alterations of EEG and frontal cognitive impairment in esophageal cancer patients complicated with depression and to assess their correlation.

Methods: Sixty-five esophageal cancer patients with depression (study group) and 62 healthy controls (control group) were included in this study. The study group were assigned into psychotic depressed (PD, $n = 32$) and nonpsychotic depressed (NPD, $n = 33$) subgroups based on complication with psychotic symptoms (Brief Psychiatric Rating Scale [BPRS] >35). EEG examination, Beck self-rating depression scale, and BPRS were used to assess clinical symptoms. Chi-square test, two independent sample *t*-test, one-way analysis of variance, and Kruskal-Wallis test were utilized to compare the variables between two groups. EEG abnormalities and scores of frontal cognitive function test were analyzed by partial correlation analysis in the PD and NPD subgroups.

Results: Compared with control group, the study group displayed greater scores either in the Stroop test (19.89 ± 2.05 vs. 24.12 ± 2.19, $P = 0.006$) or Color Trails Test (CTT; 11.92 ± 1.01 vs. 15.02 ± 1.63, $P = 0.008$), and reduced score (35.05 ± 2.01 vs. 32.11 ± 2.38, $P = 0.007$) in the verbal fluency test (VFT). Compared to NPD subgroup, PD subgroup exhibited increased scores in Stroop test (22.89 ± 2.07 vs. 25.38 ± 2.32, $P = 0.009$) and CTT (13.16 ± 1.71 vs. 15.82 ± 1.13, $P = 0.008$). Moreover, increased scores in Stroop test and CTT as well as scores in VFT were associated with the severity of depression. The study group had an abnormal frontal EEG, such as α forward, α asymmetry, α moderation, and increased θ activity relative to control group. Similarly, compared with NPD subgroup, PD subgroup displayed α forward, α asymmetry, and α moderation. The correlation test revealed that α forward and α asymmetry were negatively associated with VFT score, but positively correlated with the scores of CTT and the Stroop test in PD subgroup. In addition, α asymmetry in NPD subgroup was positively related to CTT scores.

Conclusion: This study indicated that frontal cognitive impairment in esophageal cancer patients complicated with depression is associated with EEG alterations.

Key words: Cognitive Impairment; Depression; Electroencephalogram; Esophageal Cancer; Frontal Area

Introduction

About 24% of patients with esophageal cancer are complicated with depression.[1] Previous studies showed that patients with depression have impairment of theory of mind (ToM) abilities. In the view of cognitive neuropsychiatry, ToM is divided into two components based on social information processing: social perception and social cognition.[2,3] Recently, social cognitive impairment caused by depression

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and its potential cognitive mechanisms have become a research hotspot.[4-6] Our previous report[7] revealed that esophageal cancer patients complicated with depression have social cognitive impairment. There is evidence to suggest that frontal electroencephalogram (EEG) can be used as a reliable biomarker for prefrontal-mediated cognitive functions.[8] Again, abnormal brain wave and power spectrum in depression detected by resting EEG deepen the understanding of the pathogenesis of depression, suggesting that there is a potential association between EEG activity and depression-related cognitive impairment. However, in cancer patients with depression, the alterations of frontal EEG and its relationship with cognitive impairment have to be further determined. Thus, this study aimed to investigate the association between frontal cognitive impairment and EEG changes in esophageal cancer patients complicated with depression.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Medical Ethics Committee of Changzhou No. 2 People's Hospital. All participants had provided written informed consent before recruiting into this study.

Participants

A total of sixty-five esophageal cancer inpatients complicated with depression (study group) were recruited from Changzhou No. 2 People's Hospital, the Affiliated Hospital of Nanjing Medical University between January and December, 2014. Their depression score was >5 tested by Beck Depression Inventory version-II (BDI-II).[9] All patients had at least an education of middle school. They had normal eyesight and hearing and were right handed. Exclusion criteria included no medical history of head trauma, diseases of central nervous system, metastatic brain tumor, mental illness, or substance dependence. No patient was treated with chemotherapy. Based on complication with psychotic symptoms (Brief Psychiatric Rating Scale [BPRS] >35),[10] 65 patients were further divided into two groups: nonpsychotic depressed (NPD) subgroup (33 patients) and psychotic depressed (PD) subgroup (32 patients). In addition, psychotic symptoms were distinguished from schizophrenia.

The control group included 62 healthy individuals recruited by normal physical examination. They had no history of neurological and psychiatric disorders, substance abuse, or family mental illness. The healthy individuals also had at least an education of middle school. They had normal eyesight and hearing and were right handed.

Clinical assessment and neuropsychological test

Patients were assessed by the Beck depression self-rating scale and BPRS (kappa = 0.83). All participants received Wechsler Adult Intelligence Scale (IQ) and neuropsychological tests including Color Trails Test (CTT), Stroop test, and frontal fluency test (FFT) for frontal cognitive functions.[11] CTT was used to detect visual attention and task switching. It consists of two parts: the first part is based on a numerical sequence, reflecting the right brain hemisphere function and primary sensorimotor efficiency; the second part uses a color sequence and a numerical sequence to reflect the left brain hemisphere function, including attention switching ability. The Chinese version of Stroop test was used to assess executive functions of cognitive inhibition and selective attention.[12,13] It includes four different tasks: word reading, color reading, word reading of colored word, and color naming of colored word. The completion time and the number of errors made during each task/test were recorded. The FFT, consisting of verbal fluency test (VFT) and figure fluency test (FFT), was utilized to assess the executive function and the fluency of thinking and conception in the frontal area.[14] Participants were required to tell the name of vegetable, fruit, and animal presented during VFT within 1 min. Score was recorded while participants told the correct name of vegetable, fruit, or animal only for the first time (one point for one correct name). Participants were required to draw up swiftly every presented figure during FFT within 1 min. Likewise, score was recorded only when the right picture was given for the first time (one point for one correct figure).

Electroencephalogram examination

The data of EEG examination were collected according to the international 10–20 system for electrode placement utilizing the 4418K EEG instrument (Photoelectric Co. Ltd., Japan). A total of 16 electrodes were placed over an electrode cap with plastic electrode filled of electrode gel. The electrode impedance of all electrodes was controlled under 5 kΩ. This study focused on the frontal area, and thus, the EEG signal from frontal-related electrodes was collected. Participants were required to keep awake and remain eyes closed but to stay relaxed during EEG examination. The power spectral frequency of the EEG single was quantified using the Fourier transformation function. Power was calculated in three frequency bands, corresponding to θ (4–8 Hz), α (8–13 Hz), and β (13–20 Hz).

Statistical analysis

Statistical analysis was carried out using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). On the basis of variable types, Chi-square test, two independent sample *t*-test, one-way analysis of variance (pairwise comparison by Bonferroni correction), and Kruskal-Wallis test (pairwise comparison using Mann-Whitney *U*-test) were utilized. EEG abnormalities and scores of frontal cognitive function test were analyzed by partial correlation analysis in the PD and NPD subgroups. Statistical significance was set at $P < 0.05$.

Results

Characteristics of the participations

The esophageal cancer inpatients complicated with depression aged from 28 years to 60 years, with a mean age of 48.5 ± 4.5 years. The patients obtained 9–16 years of education, with a mean period of 12.6 ± 1.6 years. The mean age of the NPD subgroup and the PD subgroup was

45.0 ± 5.0 years and 46.3 ± 4.2 years, respectively, and the mean period of education was 12.2 ± 1.1 years for NPD subgroup and 11.4 ± 1.3 years for PD subgroup. The mean age of control group was 47.7 ± 4.6 years (range: 27–60 years), and a mean education period was 11.6 ± 2.0 years (range 9–16 years).

There were no significant differences in gender, age, and education period between the study group and the control group, or between NPD and PD subgroups (all $P > 0.05$). Again, there was no significant difference in disease duration between NPD and PD subgroups (2.7 ± 0.8 years vs. 2.1 ± 1.0 years, $t = 0.69$, $P > 0.05$). BDI-II score, BPRS score, anxiety-depression factor score, and hostility-suspicion factor score in the PD subgroup were significantly higher than those in the NPD subgroup (all $P < 0.01$). There were no significant differences in other scores between the two subgroups [all $P > 0.05$; Table 1].

Comparison of frontal cognitive function scores

No obvious differences in IQ score were found between the study group and the control group ($t = 0.52$, $P > 0.05$) and between NPD and PD subgroups ($t = 0.12$, $P > 0.05$). As shown in Table 2, compared with the control group, the scores of the Stroop test and CTT were markedly higher in the study group (for Stroop test, $t = 6.14$, $P = 0.006$; for CTT, $t = 5.37$, $P = 0.008$), PD subgroup (for Stroop test, $\mu = 0.00$, $P < 0.001$; for CTT, $\mu = 1.00$, $P = 0.002$), and NPD subgroup (for Stroop test, $\mu = 0.00$, $P = 0.005$; for CTT, $\mu = 0.00$, $P = 0.007$). However, the score in the VFT was significantly reduced in the study group ($t = 6.77$, $P = 0.007$) and PD subgroup ($\mu = 1.00$, $P = 0.002$). Compared with NPD subgroup, the PD subgroup had higher scores in the Stroop test ($t = 5.32$, $P = 0.009$) and CTT ($t = 5.78$, $P = 0.008$). There was no difference in the FFT score among the study (PD and NPD) group and the control group. Based on BDI-II score, these patients complicated with depression were divided into three grades: mild (score: 14–19; $n = 22$), moderate (score: 20–28; $n = 18$), and severe (score: 29–36; $n = 15$). The results of this study showed that the severity of cognitive impairment was associated with the depression grade [Table 3].

Table 1: Comparisons of depression-related clinical symptoms between PD and NPD subgroups

Items	PD subgroup ($n = 32$)	NPD subgroup ($n = 33$)	t	P
BDI-II score	33.00 ± 4.62	20.22 ± 3.28	6.77	0.003
BPRS score	43.72 ± 7.11	27.13 ± 6.12	6.78	0.002
Anxiety-depression factor scores	14.28 ± 2.21	10.75 ± 2.69	3.56	0.004
Anergia factor score	6.13 ± 3.14	5.12 ± 3.46	0.56	0.420
Thought disturbance factor score	6.34 ± 3.35	5.91 ± 3.29	0.27	0.560
Activation factor score	4.99 ± 2.36	4.97 ± 3.01	0.14	0.920
Hostile-suspiciousness factor score	10.31 ± 2.95	2.21 ± 1.95	10.95	<0.001

The data are shown as mean ± SD. PD: Psychotic depressed; NPD: Nonpsychotic depressed; BDI-II: Beck depression inventory version II; BPRS: Brief Psychiatric Rating Scale; SD: Standard deviation.

Table 2: Comparisons of frontal cognitive functions between study and control group

Items	Study group ($N = 65$)			Control group ($n = 62$)
	Total group	PD subgroup ($n = 32$)	NPD subgroup ($n = 33$)	
IQ score	103.12 ± 5.18	103.42 ± 3.58	103.77 ± 4.30	104.11 ± 3.22
VFT score	32.11 ± 2.38*	30.02 ± 2.16†	33.21 ± 2.08	35.05 ± 2.01
Stroop test score	24.12 ± 2.19*	25.38 ± 2.32†,‡	22.89 ± 2.07†	19.89 ± 2.05
Gender recognition score	30.11 ± 1.02	30.12 ± 0.99	30.22 ± 0.95	30.57 ± 1.01
CTT	15.02 ± 1.63*	15.82 ± 1.13†,‡	13.16 ± 1.71†	11.92 ± 1.01
FFT	31.25 ± 0.68	31.31 ± 0.71	31.52 ± 0.62	31.51 ± 0.65

The data are shown as mean ± SD. *Compared with the control group, $P<0.01$; †Compared with the control group, $P<0.05$; ‡Compared with the NPD group, $P<0.01$. PD: Psychotic depressed; NPD: Nonpsychotic depressed; FFT: Frontal fluency test; VFT: Verbal fluency test; CTT: Color Trails Test; SD: Standard deviation; IQ: Intelligence quotient.

Table 3: Association between depression grade and frontal cognitive functions in the esophageal cancer patients complicated with depression

Items	Depression grade			r	P
	Mild ($n = 22$)	Moderate ($n = 18$)	Severe ($n = 15$)		
VFT	34.26 ± 2.31	31.73 ± 1.92	29.55 ± 1.63	−0.52	0.022
CTT	14.11 ± 1.22	14.98 ± 1.17	16.34 ± 1.56	0.61	0.034
Stroop test	21.98 ± 1.86	23.45 ± 1.91	26.12 ± 2.11	0.69	0.017

The data are shown as mean ± SD. Pearson's correlation analysis was performed. VFT: Verbal fluency test; CTT: Color Trails Test; SD: Standard deviation.

Table 4: Comparison of EEG alterations among the study and control groups

Items	Study group ($N = 65$)			Control group ($n = 62$)
	Total group	PD subgroup ($n = 32$)	NPD subgroup ($n = 33$)	
α forward/generalization, *n* (%)	14 (21.5)*	11 (34.4)*,†	3 (9.1)	2 (3.2)
α asymmetry, *n* (%)	17 (26.2)*	12 (37.5)*,†	5 (15.2)*	0 (0.0)
α moderation, *n* (%)	3 (4.6)*	2 (6.3)*,†	3 (9.3)*	2 (3.2)
Increased θ activity, *n* (%)	6 (9.2)*	3 (9.3)*	3 (9.0)*	2 (3.2)
Normal form, *n* (%)	25 (38.5)	4 (12.5)	21 (63.7)	56 (90.4)
Abnormal rate (%)	61.5*	87.5*	36.4*	9.6

*Compared with the control group, $P<0.01$; †Compared with NPD subgroup, $P<0.01$. EEG: Electroencephalogram; PD: Psychotic depressed; NPD: Nonpsychotic depressed.

Electroencephalogram alterations

As shown in Table 4, the rates of EEG abnormality in the frontal area, such as α forward ($\chi^2 = 29.22$, $P < 0.001$), α asymmetry ($\chi^2 = 43.26$, $P < 0.001$), α moderation ($\chi^2 = 13.54$, $P < 0.001$), and increased θ activity ($\chi^2 = 7.91$, $P = 0.005$), were significantly increased in the study group, compared with the control group. Compared to NPD subgroup, the results of EEG examination in PD subgroup showed significantly increased α forward ($\chi^2 = 44.78$, $P < 0.001$), α asymmetry ($\chi^2 = 39.57$, $P < 0.001$), and α moderation ($\chi^2 = 8.89$, $P = 0.003$).

Analysis on electroencephalogram alterations and frontal cognitive functions in the psychotic depressed and nonpsychotic depressed subgroups

After adjusting Beck depression self-rating scale, partial correlation analysis revealed that the α forward and α asymmetry in the PD subgroup were both negatively related to VFT score ($r = -0.51$, $P < 0.01$; and $r = -0.55$, $P < 0.01$, respectively), but were positively correlated with CTT score ($r = 0.53$, $P < 0.01$; and $r = 0.52$, $P < 0.01$, respectively) and Stroop test score ($r = 0.59$, $P < 0.01$; and $r = 0.57$, $P < 0.01$; respectively). Moreover, in the NPD subgroup, α asymmetry was positively associated with CTT score ($r = 0.54$, $P < 0.01$; Table 5).

Table 5: Correlation between EEG alterations and frontal cognitive functions in the PD and NPD subgroups

EEG alterations	VFT	CTT	Stroop test
α forward/generalization			
PD subgroup	−0.51*	0.53*	0.59*
NPD subgroup	−0.26	0.67	0.69
α asymmetry			
PD subgroup	−0.55*	0.52*	0.57*
NPD subgroup	0.11	0.54*	0.70

*$P<0.01$. EEG: Electroencephalogram; PD: Psychotic depressed; NPD: Nonpsychotic depressed; VFT: Verbal fluency test; CTT: Color Trails Test.

Discussion

In this study, we found that the frontal cognitive functions in the esophageal cancer patients complicated with depression were impaired tested by the Stroop test, CTT, and VFT. And, altered scores in these tests were associated with the severity of depression. Interestingly, these patients exhibited an abnormal frontal EEG. The correlation test revealed that α forward and α asymmetry were negatively associated with VFT score, but positively correlated with CTT scores and the Stroop test in PD subgroup. In addition, α asymmetry in NPD subgroup was positively related to CTT scores.

It is known that patients with cancer are always accompanied by depression, almost involving 50% of cancer patients.[15,16] A meta-analysis published in 2010[17] reported that the mortality by cancer-related depression was elevated by 22%. However, the potential mechanisms need to be clarified.[18,19] Several lines of evidences showed that the level of 8-OH-dG in peripheral serum of depression patients was significantly upregulated, suggesting that oxidative damage may be the common pathophysiological mechanism for cancer and depression.[20,21] These potential mechanisms implicate that cancer associated with depression may be not only associated with the psychological responses, but also with organic depression.

Most investigators proposed that low levels of monoamine neurotransmitters such as noradrenalin and 5-hydroxytryptamine played an important role in depression.[22,23] Nonetheless, aberrant excitatory signal transmission was found in the rodent model of depression, suggesting that depression may be caused by the inability of communication among brain cells.[24] EEG is generally considered as the sum of the postsynaptic potential of electrophysiological activity in the cerebral cortical neurons. Aberrant EEG signal results from both the alteration of neurotransmitters and neuronal signal transmission among different brain areas. A number of studies have shown that the frontal cortex exerts an important effect on human emotion and cognitive function.[25,26] Consistently, the results by neuropsychological tests in this study suggested an impaired frontal cognitive function in esophageal cancer patients complicated with depression. Along with the severity of depression, the cognitive impairment also increases. Meanwhile, the results of EEG examination in this study revealed an abnormal activity in the frontal area. The normal electrophysiology activity of the frontal area is mainly in the process of desynchronization, with most common β activity and relatively weak α activity. Knott *et al*.[27] reported that depressive patients exhibited a higher index of α power spectrum asymmetry between the left and right hemispheres

than the controls. Relative to normal controls, patients with depression or a history of depression had frequent α activity in the left frontal cortex, suggesting reduced frontal activation. Studies on emotional intelligence and resting EEG showed that higher emotional intelligence was accompanied by stronger activity in the left frontal area. Again, there was evidence that lateralization of frontal cortical activity was triggered by emotional regulation.[28] Conversely, lateralization of frontal cortical activity can influence emotional regulation and in turn may predict depression and anxiety in a certain extent. These reports were consistent with our results about increased α asymmetry. Besides pathological factors, psychological cognitive activities also leads to α forward and generalization, with a shift of α wave from the occipital area to the frontal area and further to the entire brain.[29] The increase of θ activity in the frontal area is due to frontal hypoperfusion or drowsy or nervous when taking EEG examination. Our findings further showed that there were associations between abnormal EEG activity and impaired frontal cognitive functions, and between abnormal EEG activity and frontal cognitive impairment increased with the severity of cancer-related depression. Therefore, the early examination of EEG and neurocognitive tests may be helpful for early intervention of cancer-related depression.

Notably, this study has some limitations. First, this study failed to make stratified analysis for other covariance factors, such as gender, food, and other lifestyle, as well as cancer progression. Second, this was a small-scale sample study, a further large-scale sample investigation need to be required, especially for stratified analysis. Finally, this study only analyzed the frontal EEG activity and frontal-related cognitive functions in the patients.

In conclusion, this study indicated that frontal cognitive impairment in esophageal cancer patients complicated with depression is associated with EEG alterations. EEG serves as a useful tool for clinical examination due to simple operation, convenience and economy. This study provided an EEG reference for detection of cognitive impairment in esophageal cancer patients complicated with depression. Nevertheless, it needs to be investigated whether EEG can be used as one of markers to evaluate the therapeutic efficacy for esophageal cancer patients complicated with depression.

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Conflicts of interest

There are no conflicts of interest.

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