Research Paper

Frontal asymmetry as a core feature of major depression: a functional near-infrared spectroscopy study

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Background: Frontal asymmetry plays a major role in depression. However, patients with treatment-resistant depression (TRD) have widespread hypofrontality. We investigated whether patients with TRD have a characteristic frontal activation pattern in functional near-infrared spectroscopy (fNIRS) findings and how the frontal cortex responds to different levels of cognitive tasks. **Methods:** We enrolled 27 right-handed patients with TRD, 27 patients without TRD and 27 healthy controls. We used multichannel fNIRS to evaluate activation of the bilateral dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and left motor area in response to 3 tasks: finger tapping, a low cognitive–load motor task; verbal fluency, a moderate cognitive–load task; and a dual task involving simultaneous finger tapping and verbal fluency, a high cognitive–load task. **Results:** We found significant between-group differences in left DLPFC activation for all 3 tasks. The healthy controls had cortical activation in the left motor area during finger tapping and the bilateral frontal cortex during the dual task. However, patients without TRD had right VLPFC activation during finger tapping and left DLPFC activation during the dual task. Patients with TRD had bilateral DLPFC activation during finger tapping but exhibited increased bilateral VLPFC and left motor area activation during verbal fluency and increased left motor area activation during the dual task. In healthy controls and patients without TRD, we found that the right VLPFC was positively correlated with depression severity. **Limitations:** Our cohort included only patients with late-onset depression. **Conclusion:** We found different patterns of abnormal frontal activation between patients with and without TRD. In patients without TRD, the right prefrontal cortex (PFC) was recruited during simple motor tasks. However, in patients with TRD, the bilateral PFC was recruited during simple tasks and motor cortical resources were used compensatorily during PFC-demanding complex cognitive tasks.

Introduction

Major depressive disorder is the second-leading cause of disability.[1] It has a lifetime prevalence rate of 11.3%.[2] Among patients with major depressive disorder (MDD), those with treatment-resistant depression (TRD) are the most severely disabled:[3] 50%–60% of all patients with depression have TRD.[4]

Patients with depression have prefrontal cortex (PFC) hypometabolism.[5–7] A 1993 study using MRI to examine 48 patients with severe depression reported that the mean total frontal lobe volume was 7% smaller in inpatients with severe depression than in healthy control participants.[5] Using resting-state functional magnetic resonance imaging (fMRI), a 2010 study involving 19 patients with a recent diagnosis of major depression reported reduced connectivity of the left frontal pole in a network associated with attention and working memory.[6] In addition, a 2017 study that used positron emission tomography (PET) to examine 17 patients with MDD reported that decreased cortical blood flow and standardized uptake value in the prefrontal lobe were closely correlated with depression severity.[7]

The aforementioned studies have often used fMRI or PET to evaluate PFC function. However, these techniques have high costs and low portability. Functional near-infrared spectroscopy (fNIRS) has been used instead to measure metabolism in different brain areas,[8–11] especially during cognitive performance.[12–16] The reliability of event-related fNIRS has been proven.[17] Several studies have attempted to differentiate patients with MDD from healthy people by using fNIRS,[18] especially during verbal fluency tasks.[19–23] Patients with depression have been reported to have attenuated cerebral hemodynamic changes compared with healthy people, and a higher degree

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of attenuation was associated with more severe depression.[24] However, we are unaware of any studies that have used fNIRS with verbal fluency tasks to further differentiate patients with TRD from patients with MDD without TRD.

We hypothesized that patients with TRD would have a characteristic pattern of fNIRS during a verbal fluency task. We compared 3 groups of participants: patients with TRD, patients without TRD and healthy controls. We used fNIRS to evaluate the slope over time of blood hemoglobin difference (Hbdiff) (oxygenated hemoglobin [HbO] minus deoxygenated hemoglobin [HbR]) while the participants engaged in different cognitive tasks, including finger tapping, verbal fluency and dual finger tapping and verbal fluency tasks. We applied fNIRS to the bilateral dorsolateral PFC (DLPFC) and left motor area, which are related to cognitive deficits in finger tapping and verbal fluency tasks.[25,26]

Methods

Study participants

We enrolled 81 participants, including 27 healthy controls, 27 patients without TRD and 27 patients with TRD. Psychiatric diagnosis was confirmed through the Mini-International Neuropsychiatric Interview (MINI) based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria and Thase and Rush staging of treatment resistance (stage ≥ 2). All participants were drug naive or drug free for at least 1 week. Healthy controls did not have major medical or neurologic illnesses, a history of alcohol or substance abuse, or a diagnosis of psychiatric disorder, as determined using the MINI. Exclusion criteria for the initial enrollment included not being a native Chinese speaker and being unfamiliar with Mandarin phonetic symbols. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of Taipei Veterans General Hospital. Informed consent was obtained from all participants before all assessments.

Clinical psychiatric and symptomatic evaluations

We completed detailed psychiatric and medical histories and a diagnostic interview using the MINI for all participants. Handedness among the participants was confirmed using the Edinburgh Handedness Inventory.[27] All participants were right-handed. We evaluated depression symptoms using the 17-item Hamilton Depression Rating Scale (HDRS-17).[28] We also conducted a Wisconsin Card Sorting Test (WCST) to evaluate the cognitive function of these patients. After clinical evaluations, all participants performed the finger tapping, verbal fluency and dual task assessments and then underwent fNIRS (mentioned subsequently). Cap positioning for fNIRS was by matching the Cz point (head landmark) using the International 10–20 system criteria.

For the finger tapping assessment, participants were verbally instructed to perform a self-paced unilateral finger tapping (finger-to-thumb opposition movement, from the first to fourth finger then backward) using their dominant hand until instructed to rest (about 20 s).

For the verbal fluency assessment, participants were asked to generate a maximal number of words starting with a Chinese phonetic symbol (e.g., /b(ㄅ)/, /p(ㄆ)/, /m(ㄇ)/, /f(ㄈ)/, /d(ㄉ)/, /t(ㄊ)/) within 20 seconds. Word generation and counting were recorded during the task. To ensure sufficient compliance, each participant had adequate practice trials before the assessment.

For the dual task assessment, participants were instructed to perform finger tapping and verbal fluency simultaneously within a task session. They were asked to generate as many words as possible while tapping their finger for about 20 seconds; the task ended with a resting instruction.

Measuring cerebral activity using functional near-infrared spectroscopy

To estimate the signal-to-noise quality of a data channel, we calculated the relative coefficient of variation (CV, %) for the raw signals at 760 and 850 nm, which is a routine procedure for fNIRS measurement.[29] We implemented data rejection based on 2 types of CV (CVchan and CVtrial) to reduce physical artifacts, such as motion-induced instabilities and blood pressure–induced hemodynamics.[30]

$$\text{CVchan} = \sigma/\mu \times 100\%$$

where μ is the mean and σ is the standard deviation of the signal. We calculated CVchan over the duration of the assessment (about 18 min) for each channel, and we rejected measurement channels with a value of CVchan greater than 15%. We then obtained CVtrial for 20-second intervals of the individual trial block, and only trials for each remaining channel (CVchan < 15%) with a value of CVtrial less than 10% in both wavelengths were used for subsequent analyses.

The remaining fNIRS signals were bandpass filtered (only frequencies between 0.01 and 0.05 Hz were used) to eliminate the effects of heartbeat, respiration and low-frequency signal drifts for each wavelength.[30] We performed wavelet filtering to correct for the motion artifacts in each channel. In this filtering process, the measured signal is typically assumed to be a linear combination of the physiologic signal of interest (hemodynamics) and motion artifacts. Because hemodynamic responses are considerably slower than motion artifacts (such as a spike artifact), the wavelet coefficients for the evoked responses are anticipated to be a Gaussian probability distribution with zero mean and low variance; however, the outliers are assumed to account for the motion artifacts. The outlying coefficients (those exceeding a predefined threshold) can be eliminated before signal reconstruction by using the inverse discrete wavelet transform to eliminate the corresponding motion artifacts. In this study, we set the removal threshold for the wavelet coefficient (α) to 0.1.[31]

We converted the preprocessed signals to HbO and HbR concentrations by using the modified Beer–Lambert law for each source–detector channel.[32] Next, we employed correlation-based signal improvement to improve the signal

quality on the basis of findings that brain activation involves HbO increases and HbR decreases in the activated cortical regions.[33] We calculated the relative changes in HbO and HbR concentrations at each time point on the basis of a 5-second baseline (about 31 frames) and collected before proceeding with each task and then averaged over 3 repetitions for each condition. We then calculated Hbdiff (HbO – HbR) to determine the increase in total hemoglobin over the initial 5-second time period after the start of the tasks (right after the task instruction and the timer started). Neuronal activation typically induces an increase in the cerebral metabolic rate of oxygen with a larger compensatory increment of local cerebral blood flow based on neurovascular coupling.[34] Cortical activation–related hemodynamic responses typically involve a rapid elevation of ΔHbO and a lower-amplitude reduction in ΔHbR, as confirmed by simultaneous applications of other neuroimaging techniques.[35] We used the slope ($\Delta(HbO - HbR)/\Delta t$) of the curve during the initial 5 seconds to represent the regional neuronal activation.

The bilateral DLPFC, ventrolateral PFC (VLPFC), and left motor and premotor areas were our primary regions of interest. The DLPFC is associated with executive function, VLPFC is a classic language area, and left motor and premotor areas are responsible for right-hand finger tapping. We executed fNIRS signal preprocessing — including bandpass filtering; motion artifact correction; and HbO, HbR and Hbdiff calculation — by using the HOMER2 package.[36] Homemade scripts developed on MATLAB (MathWorks, Natick, MA, USA) were used to calculate signal CVs and perform quantitative analyses.

Statistical analysis

We used SPSS 26.0 (SPSS, Chicago, IL, USA) for all statistical analyses. Only participants with 84.9% qualified channels were included, and the missing rate was only 4%. We used independent *t* tests and an analysis of variance (ANOVA) to compare the continuous variables (e.g., age, symptom ratings, word counts for verbal fluency and dual task, and Δ[Hb]) between 2 and 3 groups, respectively. We applied the χ^2 test to compare categorical variables between the groups. We set statistical significance at $p < 0.05$ and conducted least significant difference (LSD) tests for post hoc comparisons. Before executing the independent *t* tests and ANOVA, we used the Levene test for homogeneity of variances to confirm our homogeneity assumption. When the results obtained from the Levene test were significant ($p < 0.05$), we used independent *t* tests with equal variances not assumed for correction; we also applied the Kruskal–Wallis test (nonparametric analysis) for between-group comparisons. Statistical significance was also set at $p < 0.05$. After confirming the statistical significance between groups, we used an analysis of covariance to exclude possible confounding factors such as age, sex and HDRS-17 scores. Finally, we performed a Pearson correlation analysis to test the association between Hb values and cognitive tasks (i.e., finger tapping, verbal fluency and dual task) and between Hb and HDRS-17 scores (which reflected the severity of depression, applied to all participants).

Results

Clinical characteristics, symptom ratings and cognitive ratings among groups

We found no significant intergroup difference in terms of demographic variables such as age and sex. In addition, the duration of illness did not differ significantly between patients with and without TRD. Depressive symptoms measured using HDRS-17 differed significantly between the groups, which shows that patients with TRD had the most severe depression (mean HDRS-17 score for healthy controls 1.3, 95% CI 0.7–2.0; for patients without TRD 7.0, 95% CI 4.8–9.3; and

Table 1: Demographic, clinical and neurocognitive characteristics of study participants*

Characteristic	Healthy controls	Patients without TRD	Patients with TRD	ANOVA, F/χ^2	*p* value (ANOVA)	LSD	*p* value (Kruskal–Wallis test)
Age, yr	65.6 ± 7.7	65.3 ± 8.5	66.5 ± 6.0	0.179	0.8	–	–
No. (%) female	21 (77.8)	21 (77.8)	22 (81.5)	0.149	0.9	–	–
Duration, yr	–	12.2 ± 9.7	15.8 ± 14.3	1.152	0.3	–	–
HDRS-17 score	1.3 ± 1.7	7.0 ± 5.7	21.1 ± 9.5	67.208	< 0.001	Healthy controls < patients without TRD < patients with TRD	< 0.001
Finger tapping (times)	26.0 ± 6.5	23.7 ± 6.9	20.7 ± 9.2	3.144	0.05	Healthy controls > patients with TRD	–
Verbal fluency (word counts)	3.8 ± 2.1	3.1 ± 2.0	2.7 ± 2.0	2.050	0.1	–	–
Dual task (word counts)	4.2 ± 2.4	3.0 ± 1.9	2.9 ± 1.9	2.940	0.06	Healthy controls > patients with TRD	–
WCST, % error	47.38 ± 20.58	47.40 ± 17.90	57.56 ± 21.63	2.287	0.1	–	–
WCST, % conceptual level	37.35 ± 26.40	38.48 ± 23.58	27.22 ± 25.97	1.610	0.2	–	–
WCST, category completed	2.27 ± 2.38	2.93 ± 2.09	1.48 ± 2.01	3.023	0.05	–	–

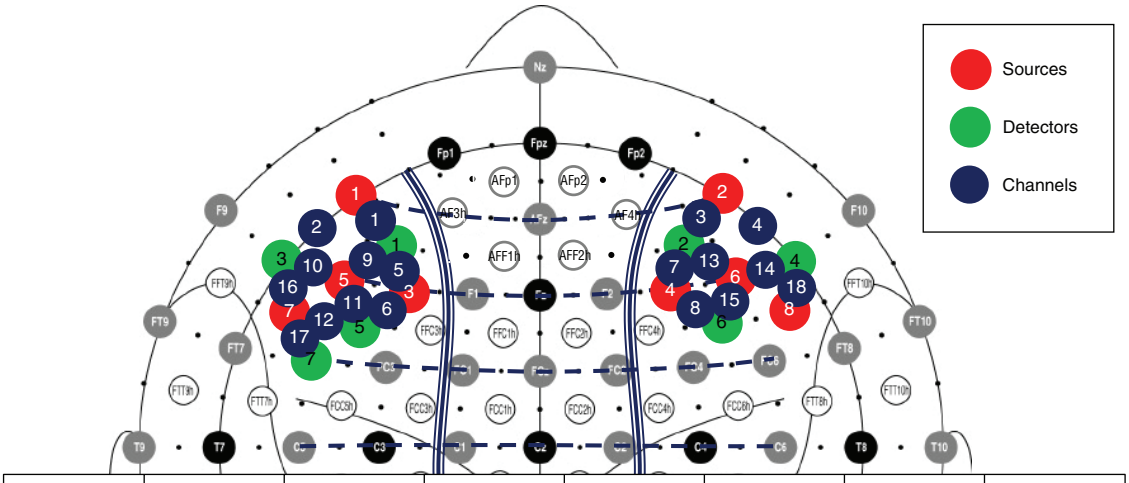
ANOVA = analysis of variance; HDRS-17 = Hamilton Depression Rating Scale (17 items); LSD = least significant difference; TRD = treatment-resistant depression; WCST = Wisconsin Card Sorting Test.
*All data are given as means ± SDs unless specified otherwise.

for patients with TRD 21.1, 95% CI 17.4–24.9). Furthermore, the 3 groups differed significantly in finger tapping but not in verbal fluency or the dual task (slower finger-tapping movement in patients with TRD than for healthy controls; however, the difference became smaller when performing the dual task). Our post hoc analysis showed that healthy controls performed finger tapping better than patients with TRD. However, results from the WCST showed a significant difference between the groups for WCST scores for categories completed but not in percent errors or percent conceptual-level responses (Table 1).

Regarding the fNIRS findings, we found significant between-group differences in the left anterior DLPFC (channel 5) for finger tapping, left posterior DLPFC (channel 11) for verbal fluency and left motor areas (channel 12) for the dual task. Post hoc analysis showed that patients without TRD exhibited attenuated oxygenation responses in the left anterior DLPFC (channel 5) for finger tapping compared with the other 2 groups. Patients without TRD also exhibited greater oxygenation responses for the left posterior DLPFC (channel 11) for verbal fluency than those in the other 2 groups. Patients with TRD exhibited lower oxygenation responses in the left motor areas (channel 12) for the dual task than healthy controls and patients without TRD (Figure 1).

We found a positive correlation between finger tapping-and fNIRS findings in the left motor area (channel 17) in healthy controls; we also found a positive correlation between the dual task and fNIRS findings in channels involving the right VLPFC and left DLPFC (channels 3, 11 and 14). In patients without TRD, we observed a positive correlation between finger tapping and the right VLPFC (channel 3) and between the dual task and the left DLPFC (channel 9). In patients with TRD, we detected a positive correlation between finger tapping and both the left DLPFC (channel 5) and the right DLPFC (channel 13); however, we noted a negative correlation between verbal fluency and the left VLPFC (channel 2), left VLPFC (channel 10), right VLPFC (channel 14) and left motor area (channel 17), and a negative correlation between the dual task and the left motor area (channel 17) (Table 2).

Our Pearson correlation analysis showed a positive correlation between HDRS-17 and Hbdiff slope for finger tapping in healthy controls and patients without TRD. We found that a higher HDRS-17 score was associated with greater recruitment of the right VLPFC. However, no such correlation was noted in patients with TRD (Table 3 and Figure 2).



	S1-D3 (Ch.2)	S1-D (Ch.1)			S2-D2 (Ch.3)	S2-D4 (Ch.4)	
S7-D3 (Ch.16)	S5-D3 (Ch.10)	S5-D1 (Ch.9)	S3-D1 (Ch.5)	S4-D2 (Ch.7)	S6-D2 (Ch.13)	S6-D4 (Ch.14)	S8-D4 (Ch.18)
S7-D7 (Ch.17)	S5-D7 (Ch.12)	S5-D5 (Ch.11)	S3-D5 (Ch.6)	S4-D6 (Ch.8)	S6-D6 (Ch.15)		

PFC + inferior frontal cortex with short distance setup

Figure 1: Areas of the brain with corresponding functional near-infrared spectroscopy channels. PFC = prefrontal cortex.

Discussion

We found significant differences in Hbdiff fNIRS activation in the left DLPFC between healthy controls, patients without TRD and patients with TRD. Our findings show that patients without TRD exhibited attenuated oxygenation responses in the left anterior DLPFC (channel 5) compared with those in the other 2 groups; however, in the left posterior DLPFC (channel 11) for verbal fluency, patients without TRD exhibited greater oxygen responses than those in the other 2 groups. In the left motor areas (channel 12) for dual task, patients with TRD exhibited lower oxygen responses than healthy controls and patients without TRD.

By using correlation tests between task performance and fNIRS findings, we observed different patterns of abnormal frontal activation between HCs and patients with and without TRD. The patients without TRD used the right PFC when engaging in simple motor tasks, whereas those with TRD used both PFCs; when engaging in PFC-demanding complex cognitive tasks, patients with TRD compensatorily used motor cortical resources.

Table 2: Correlation between task performance and functional near-infrared spectroscopy

Task	Area of the brain (fNIRS channel)	Pearson correlation	*p* value
Finger tapping			
Healthy controls	Left motor area (channel 17)	0.493	0.02
Patients without TRD	Right VLPFC (channel 3)	0.652	0.002
Patients with TRD	Left DLPFC (channel 5)	0.446	0.05
	Right DLPFC (channel 13)	0.500	0.025
Verbal fluency			
Healthy controls	–	–	–
Patients without TRD	–	–	–
Patients with TRD	Left VLPFC (channel 2)	–0.845	0.000
	Left VLPFC (channel 10)	–0.546	0.02
	Right VLPFC (channel 14)	–0.519	0.02
	Left motor area (channel 17)	–0.508	0.02
Dual task			
Healthy controls	Right VLPFC (channel 3)	0.421	0.045
	Left DLPFC (channel 11)	0.429	0.03
	Right VLPFC (channel 14)	0.416	0.04
Patients without TRD	Left DLPFC (channel 9)	0.532	0.01
Patients with TRD	Left motor area (channel 17)	–0.469	0.04

DLPFC = dorsolateral prefrontal cortex; HDRS-17 = Hamilton Depression Rating Scale (17 items); fNIRS = functional near-infrared spectroscopy; VLPFC = ventrolateral prefrontal cortex.

Table 3: Correlation between the Hamilton Depression Rating Scale (17 items) and functional near-infrared spectroscopy findings during assessment of finger tapping

Patient group, task	Area of the brain (fNIRS channel)	Pearson correlation	*p* value
Healthy controls			
Finger tapping	Right VLPFC (channel 3)	0.474	0.02
	Left motor area (channel 17)	0.452	0.03
Verbal fluency	Right motor area (channel 18)	–0.426	0.04
Dual task	–	–	–
Patients without TRD			
Finger tapping	Right VLPFC (channel 4)	0.490	0.02
	Right VLPFC (channel 14)	0.481	0.03
	Right DLPFC (channel 15)	0.591	0.005
Verbal fluency	Left DLPFC (channel 5)	–0.533	0.009
	Left motor area (channel 17)	–0.697	0.001
Dual task	Left VLPFC (channel 10)	0.518	0.02
Patients with TRD			
Finger tapping	–	–	–
Verbal fluency	Right motor area (channel 18)	–0.511	0.03
Dual task	Right DLPFC (channel 7)	–0.485	0.03

DLPFC = dorsolateral prefrontal cortex; fNIRS = functional near-infrared spectroscopy; TRD = treatment-resistant depression; VLPFC = ventrolateral prefrontal cortex.

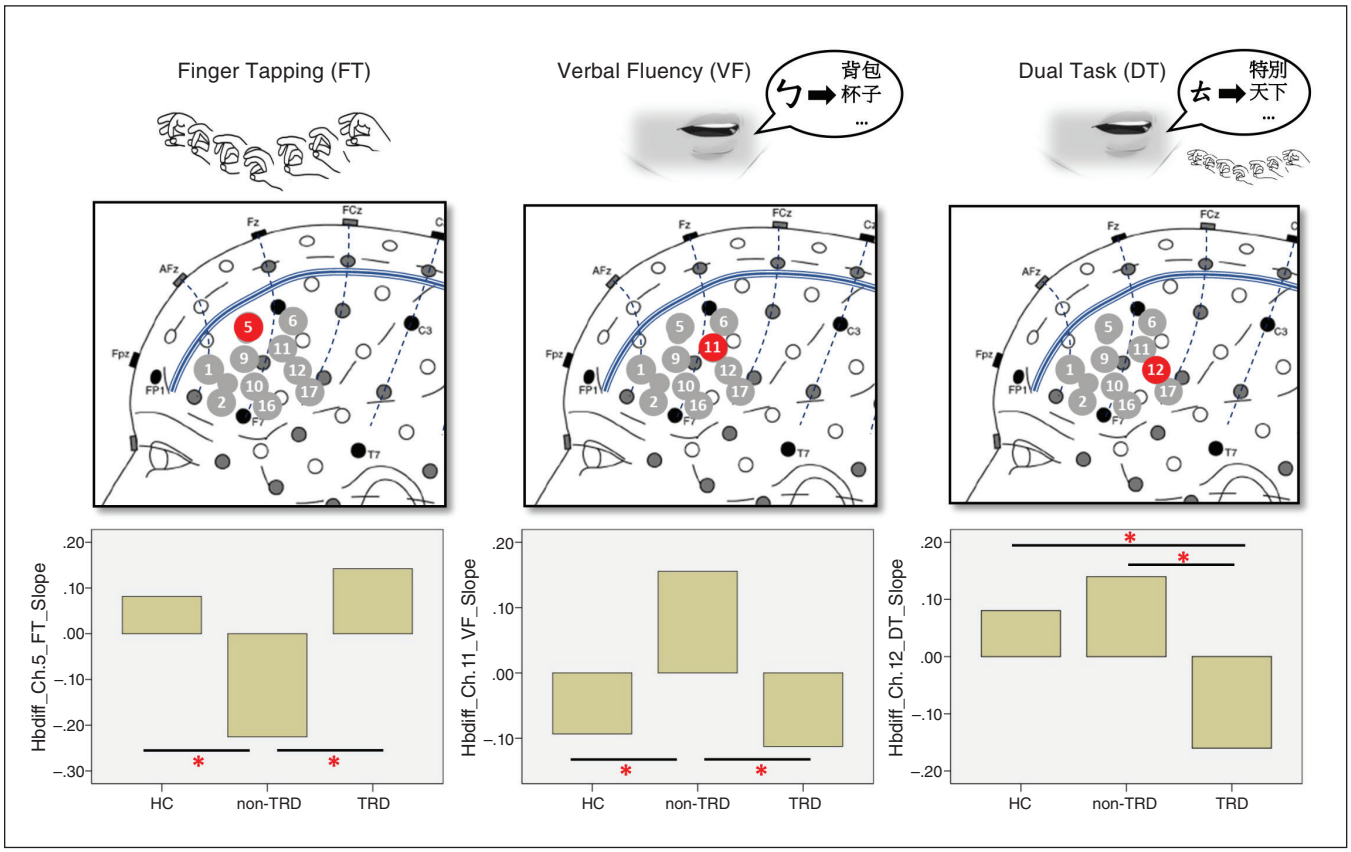


Figure 2: Differential pattern of fNIRS during assessments of finger tapping, verbal fluency and the dual task (finger tapping and verbal fluency) between groups. At the left anterior DLPFC (channel 5) during finger tapping, patients without TRD show attenuated oxygenation response compared with the other 2 groups. At the left posterior DLPFC (channel 11) during verbal fluency, the oxygenation response in patients without TRD was greater than in the other 2 groups. At the left motor areas (channel 12) during DT, patients with TRD showed decreased oxygenation compared with both healthy controls and those without TRD. The asterisk indicates significant post hoc differences. DLPFC = dorsolateral prefrontal cortex; fNIRS = functional near-infrared spectroscopy; TRD = treatment-resistant depression.

In contrast to the findings for healthy controls, our results showed significant correlations between finger tapping and the right VLPFC (channel 3) in patients without TRD (Table 2), which suggests an early and overinvolvement of the PFC in handling simple motor tasks. We examined brain activation during tasks ranging from simple to complex and observed that in healthy controls, simple tasks such as finger tapping activated the left motor area (which is reasonable because this area is associated with the movement of the right finger), and complex tasks such as the dual task activated both the left DLPFC and the right inferior frontal cortex (IFC). In patients without TRD, the right PFC was already activated during finger tapping. We excluded false discovery because even if we removed the data that were only marginally less than the 0.05 threshold, these conclusions would hold true.

We determined that in healthy controls, HDRS-17 scores were positively correlated with increased right VLPFC activation during finger tapping (Table 3). This finding supports early involvement of the right PFC in depression.

Using fMRI, a 2018 study involving 22 patients with depression and 15 healthy controls in China reported that depression was related to a dominant right hemisphere.[37] A 2008 study of prefrontal brain activation during multiple tasks in patients with MDD also applied fMRI and reported that patients with depression exhibited increased right prefrontal activation during the execution of several types of cognitive tasks.[38] The finding from a 2020 study involving 282 patients with major depression in China is consistent with the hypothesis that the right inferior frontal gyrus, projected to premotor cortical areas, is involved in depression.[39] Electroencephalogram studies have also established frontal α[40] and θ[41] asymmetry as biomarkers of depression.

We also found that patients with TRD used the bilateral PFC abnormally to cope with simple motor tasks and used motor cortical resources compensatorily when dealing with complex PFC-demanding cognitive tasks. These findings show that patients with TRD had different patterns of brain activation than patients without TRD; therefore, TRD may be caused by abnormal PFC activation sequences. In patients with TRD, expending greater effort to execute complex tasks such as the dual task resulted in more inefficient activation of the motor cortex; this implies that patients with TRD were using an incorrect strategy to solve the complex problem. The early and abnormal involvement of the bilateral PFC in

the simple task may be caused by a decline in prefrontal function in patients with TRD.[42]

A 2007 study in the United States that used fMRI and involved 21 patients with MDD suggested that a key feature underlying the pathophysiology of major depression is the counterproductive engagement of the right PFC and the lack of engagement of the left lateral–ventromedial prefrontal circuitry important for the downregulation of amygdala responses to negative stimuli.[43] We noted a similar phenomenon in patients without TRD, in whom the right PFC, rather than the left PFC, was engaged. However, we found that the left PFC was ineffectively engaged in patients with TRD.

With higher depression scores, we also observed that the right VLPFC was recruited more in healthy controls and patients without TRD. Thus, the healthy controls who were depressed had the same pattern of fNIRS as the patients without TRD: recruitment of the right VLPFC during finger tapping and verbal fluency tasks. This finding implies that otherwise healthy people and patients without TRD (but not those with TRD) share the same mechanism of depression and may lie on the same spectrum of depression.

A 2013 study that used patient data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) randomized clinical trial to calculate Individual Burden of Illness Index for Depression reported that patients with cognitive restoration had a lower relapse rate than did those without cognitive restoration.[44] Repetitive transcranial magnetic stimulation (rTMS) effectively improves cognitive function in both patients with depression and older adults.[45–47] Traditionally, rTMS has been used to target the left DLPFC with high-frequency stimulatory pulses. However, low-frequency inhibitory pulses over the right DLPFC were also reported.[48] Our study findings support that right VLPFC inhibitory rTMS might be effective in patients without TRD, and stimulatory rTMS over the left DLPFC or inhibitory rTMS over the left motor area might be beneficial in patients with TRD.

Limitations

Our cohort included only patients with late-onset depression. Whether our results can be extended to younger patients requires further research. fNIRS data are functional data, which means that we could perform fNIRS only when the patient was executing a task. Future studies should compare fNIRS data with resting-state measurements such as fMRI.

Conclusion

We observed a distinct pattern of left DLPFC activation for all 3 tasks (verbal fluency, finger tapping and the dual task) using fNIRS in healthy controls, patients without TRD and patients with TRD. The results also show right-brain activation in patients without TRD during simple motor tasks such as finger tapping and a whole-brain breakdown in patients with TRD when the tasks became difficult. Our findings suggest that inhibitory rTMS of the right VLPFC in patients without TRD might be effective, and stimulatory rTMS over the left DLPFC or inhibitory rTMS over the left motor area in patients with TRD might be beneficial.

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Competing interests: None declared.

Contributors: Cheng-Ta Li conceived and designed the work. Mu-Hong Chen, Chih-Ming Cheng, Jia-Shyun Jeng and Shih-Jen Tsai aquired the data. Jui-Wen Chu, Chia-Feng Lu and Hsiang-Jung Tseng analyzed or interpreted the data. Jui-Wen Chu, Cheng-Ta Li and Hsiang-Jung Tseng wrote the manuscript. Mu-Hong Chen, Chih-Ming Cheng, Jia-Shyun Jeng, Chia-Feng Lu and Shih-Jen Tsai critically reviewed the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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