MEDDOCS Open Access Publisher

ISSN: 2639-9237

Journal of Case Reports and Medical Images

Open Access | Research Article

Potential of Functional Near-Infrared Spectroscopy for Diagnostics of Depression

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Received: Feb 15, 2023

Accepted: Mar 07, 2023

Published Online: Mar 14, 2023

Journal: Journal of Case Reports and Medical Images

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: fNIRS; Major depressive disorder; Depress; Mood disorder; Affective disorder.

Abstract

Objective: There is lack of accurate methods to diagnose Major Depressive Disorder (MDD), one of the most prevalent global psychiatric disorders. Possible pathophysiological effects could be used in assessment of depression, and for this purpose Electroencephalography (EEG) and Functional Magnetic Resonance Imaging (fMRI) are being studied. In addition, Functional Near-Infrared Spectroscopy (fNIRS) shows promising results as a method to assess MDD. In 2020, a total of 64 fNIRS studies on depression between 1980-2019 were reviewed. Since then, over 100 fNIRS studies were conducted between 2019-2022. This work aims to systematically review selected fNIRS studies conducted between 2019 and 2022 on MDD, in correlations with depression symptomatology, and in the monitoring the outcome of the treatment.

Methods: PubMed was search for published English articles from 2019 to 2022 that diagnosed depression using fNIRS, correlated fNIRS data with depressive symptoms, and monitored treatment outcome in depressed patients based on a defined inclusion and exclusion criteria.

Results: A total of 50 studies were selected. MDD individuals generally showed reduced hemodynamic response in the left prefrontal cortex compared to healthy controls. Generally, a negative correlation between overall depressive symptom severity and frontotemporal cortex oxygenated hemoglobin (HbO) levels was found. HbO changes were generally observed in various type of treatments.

Conclusions: This work provides an update of fNIRS application in MDD diagnostic and prediction from 2019 to 2022. Monitoring cerebral hemodynamics by fNIRS could be a potential method for diagnosis and assessment of treatment outcome of MDD.

Cite this article: Triana R, Saara R, Teemu M. Potential of Functional Near-Infrared Spectroscopy for Diagnostics of Depression. J Case Rep Clin Images. 2023:6(1): 1134.

Introduction

Depression, more specifically major depressive disorder (MDD), is one of the most prevalent psychiatric disorders worldwide and a significant cause of health loss and disability, estimated by WHO to affect over 300 million people globally [1]. Its symptoms include persistent depressed mood and loss of interest or pleasure in activities, as well as sleep-related problems, changes in appetite, fatigue or loss of energy, feelings of guilt or worthlessness, as well as cognitive and psychomotor dysfunction and, in the most severe cases, recurring suicidal thoughts or suicide attempts [2].

Depression can be divided into more specific subtypes such as seasonal affective disorder, treatment resistant depression and dysthymia, a less intense but more long-lasting form of depression. Depression can even occur with psychotic or catatonic symptoms [2,3]. MDD is sometimes referred to as unipolar depression to differentiate from bipolar depression which occurs as part of bipolar disorder (BD). Given that the depressive symptoms are similar in both disorders, differentiating MDD from BD can be a clinical challenge.

MDD is generally diagnosed based on subjective assessment using diagnostic criteria and rating scales that measure symptom severity, which can make diagnosing depression challenging and lead to inaccurate diagnoses. Currently, there are no objective tools or biomarkers to aid the diagnosis of depression in general clinical use.

The most typical treatments of depression are psychotherapy and antidepressant medications that affect the serotonin, norepinephrine, and dopamine systems of the brain. In severe or treatment-resistant depression, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or ketamine-like drugs can be effective [2].

Possible pathophysiological mechanisms of depression include alterations in the monoaminergic systems of the brain, as well as abnormal function of brain regions such as the ventral paralimbic structures and prefrontal cortex [2]. These brain alterations have been studied with different brain imaging methods such as electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and more recently, functional near-infrared spectroscopy (fNIRS).

In recent years, an increasing number of studies have been made using fNIRS to observe alterations in brain oxygenation in major depressive disorder. Ho et al. [4] have systematically reviewed research related to applications of fNIRS for major depressive disorder up until 2019. In this review, a similar approach has been used for studies published starting 2019. The aim of this review is to cover new research on the applications of fNIRS as a tool for diagnosing depression, screening for, and assessing depressive symptoms, as well as monitoring treatment outcome in depressed patients.

Methods

Information Sources and Search Strategy

A search was conducted on PubMed on July 10th, 2022. The following string of keywords was used: *"near-infrared spectroscopy" OR "nirs" OR "fNIRS" AND ("depress*" OR "mood disorder" OR "affective disorder").* The search was limited to studies published in English between 2019-2022.

Eligibility Criteria and Selection of Sources

Studies were included if they included subjects of any age group with major depressive disorder or depressive symptoms assessed with appropriate diagnostic tools and if they used fNIRS to examine brain hemodynamic response. Studies were excluded if they were deemed to have a wrong study design, a patient population with an irrelevant diagnosis or insufficient depressive symptoms, or if no full text was accessible. Case reports and studies with a sample size < 5 were also excluded. The literature search is illustrated in the flow chart in **Figure 1**.

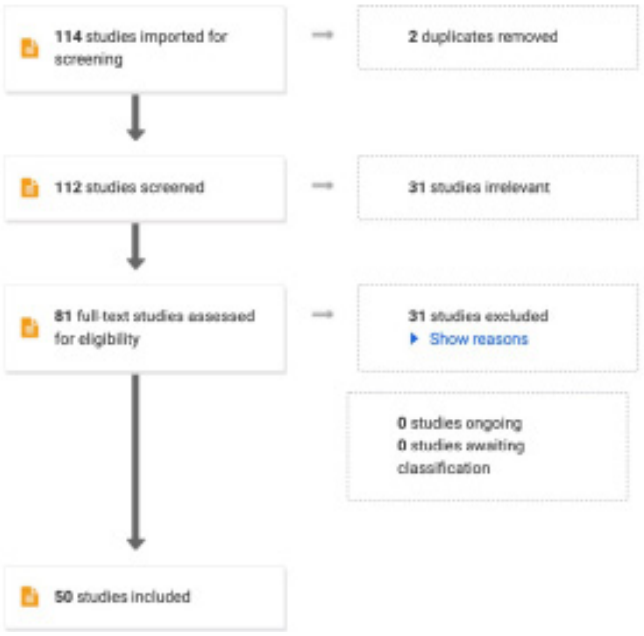

Figure 1: Literature search flow chart.

Results

Selection of Sources

The search on PubMed yielded 114 results in total. After duplicate removal, 112 studies proceeded to title and abstract screening and 81 further to full text review. Fifty studies in total were chosen for data extraction and included in this review.

Three Categories of The Studies

Studies were then sorted into three categories based on their aim: (1) diagnosing depression using fNIRS, (2) correlating fNIRS data with depressive symptoms, and (3) monitoring treatment outcome in depressed patients.

Most of the studies utilized continuous-wave NIRS systems with a few utilized time-domain NIRS, spread spectrum modulation direct sequence NIRS, and spatially resolved NIRS systems. Those systems provided measurement of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR). However, most of the studies focused more on the change in HbO.

Diagnosing Depression: Differentiating Depression from Other Disorders and Healthy Individuals

Twenty-three studies were identified utilizing NIRS to differentiate depressed patients from healthy controls (HCs) and/or patients with other psychiatric disorders. Most of the studies were conducted in Asia with China (n = 8), Japan (n = 7), and Singapore (n = 5) contributing mostly to the number, followed by Taiwan, South Korea, and the USA. A total of 2,585 participants comprised the sample consisting of 975 HCs, 790 MDD patients,

and 820 patients with other psychiatric disorders. Most of the studies utilized DSM-5 as the diagnostic criteria, with 4 studies utilizing DSM-IV and the exception of 2 studies that provide no information on the diagnostic criteria used. Mostly the Hamilton Depression Rating Scale (HAMD) was used as the psychopathology measure. Apart from 7 studies that included large number of depressed patients and did not include an indication of medication consumed by the patients, and 4 studies that included medication-free patients with/without a time limit, most depressed patients received medications in which 7 studies reported varied type of medication consumed such as antidepressants, anxiolytics, antipsychotics, sedatives or mood stabilizers. Most studies utilized verbal fluency test (VFT) as the activation task, while the others adopted finger tapping, the combination of VFT and finger taping, facial recognition, emotional face recognition task, emotional intensity rating task, working memory task, emotional Stroop task, sound stimuli paradigm, high-level cognition task, Tower of London (TOL), resting state and non-task. The NIRS devices and the number of channels utilized varied across studies, with a large proportion using the 52-channel ETG-4000. Most of the studies measured the frontal (especially prefrontal) and temporal areas, except for 1 study that measured the whole cerebral cortex.

Individuals with MDD were generally found to have a reduced hemodynamic response compared to HCs. Husain et al. [5] and Ong et al. [6] found it in MDD frontal temporal area, and even MDD showed reduced metabolite concentrations via amino acid profiling [6]. Gao et al. [7] and Hu et al. [8] specifically found that in the left prefrontal cortex. Chao et al. [9] revealed that MDD patients showed abnormalities in functional connectivity, and in bilateral ventrolateral prefrontal cortex (VLFPC) and bilateral dorsolateral prefrontal cortex (DLPFC) blood oxygenation compared to HCs. MDD patients also showed significantly different patterns of prefrontal functional connectivity compared to HCs during VFT [10]. When subjects were exposed to unfavorable stimuli, hyperactivated HbO was observed in the left frontal cortex of MDD patients [11]. Tseng et al. [12] investigate the characteristic of frontal activation pattern in 3 different group: HCs, MDD patients with treatment-resistant depression (TRD), and MDD without TRD. Significant frontal activation patterns in left DLPFC were found among them. As depressed individuals often perceive neutral facial expression as emotional, Manelis et al. [13] investigated the ability of depressed group with MDD/Bipolar I/Bipolar II to identify facial emotional expression. It was found that depressed perform slower and less accurate compared to HCs, and lower right prefrontal cortex (PFC) activation in depressed was associated with the lower accuracy for neutral facial emotional expression recognition. Atsumori et al. [14] developed a PFC measurement technique to assess the mental state quantitatively and objectively. The PFC activation of the return-to-work trainees in remission of mental disorders with depressive symptoms and of HCs were observed. It was found that the PFC activation indicates a healthy state and can be used to distinguish both.

Studies have also observed different hemodynamic activation patterns in MDD patients compared to those with bipolar disorder (BD), schizophrenia (SCH), borderline personality disorder (BPD), generalized anxiety disorder (GAD), or comorbid anxiety and depression (A&D). SCH patients showed significantly decreased hemodynamic changes in DLPFC [15] and exhibited reduced anterior prefrontal blood volume [16] compared to MDD. BPD patients showed a higher hemodynamic response in the right frontal cortex compared to MDD [17]. As MDD patients and GAD patients are frequently comorbid with each other (CMG), Hu et al. [16] investigated the cognitive functions of their PFC. Significant hypo-activation at the middle frontal pole cortex was found in MDD patients compared to CMG. However, the study cannot establish significant differences between MDD and GAD patients. Wen et al. [18] explored the characteristic markers of MDD and A&D. It was found that the spectral analysis of A&D patients' brain oxygenation was characterized by an intermediate peak in spontaneous low-frequency oscillations in the magnitude spectrum when performing the VFT task. In case of differentiating MDD from BD, generally it is difficult to distinguish their depressive mood state. Tsujii et al. [19] investigated the association between left frontopolar hemodynamic response and mitochondrial DNA copy number, and found that their association has the potential as a marker to distinguish MDD from BD.

One study explored the characteristics of hemodynamic changes in the PFC of patients with bipolar depression (BD) and unipolar depression (UD). Feng et al. [20] found that UD patients showed reduced hemodynamic activation changes in the VLPFC area compared to BP.

Differences in hemodynamic response between depressed and non-depressed adolescents with the autism spectrum (ASD) have also been observed. Ohtani et al. in [21] observed reduced activation in broad frontotemporal areas in both ASD groups compared to the TD group. They even found it specifically in the right VLPFC and it was further found that ASD adolescents with depression showed reduced activation in the right anterior temporal cortex (aTC) [22].

Some of the studies focused on comparing different activation tasks or finding the most effective analytic methods for differentiating depressed individuals from healthy ones. Wen et al. [18] found that non-task is insufficient in differentiating depressed patients from HCs. Lang et al. [23] found that high-level cognitive task (HCT) would activate more oxygenation changes in the cerebral cortex of A&D patients compared to VFT. This suggests that HCT performs better and has the potential to evaluate the therapeutic effects for A&D patients. Xiang et al. [15] revealed that PFC activation was more extensive during the VFT than during the TOL task in SCH and MDD patients. Ho et al. [24] explored machine learning algorithms to improve the diagnostic accuracy of MDD. Their multimodal machine learning model yielded the highest diagnostic accuracy for MDD compared to the unimodal and bimodal models.

One study evaluated NIRS to measure the resting-state functional connectivity (RSFC) in MDD [25] compared to previous fMRI studies. It was found that NIRS can partially detect abnormalities in RSFC patterns in MDD. This suggested that NIRS-based measurements of RSFCs have potential clinical applications. In effort to investigate fNIRS as a clinically viable tool to distinguish depressed from HCs, Wei et a. [26] found that a combined index of Integral Value of R1 and Centroid Value of R2 can better distinguish individuals with mood disorders from HCs than SCH. These results inform that fNIRS can be used as a candidate biomarker.

As the early diagnosis of MDD is very important, Li et al. [27] studied the cortical hemodynamic response from MDD to identify the objectively measurable biomarkers. The abnormal PFC activity of MDD may be quantified as a diminished relative intensity and inappropriate activation timing of the hemodynamic response.

Correlating fNIRS Data with Depression Symptoms

Fourteen studies examined the relationship between fNIRS signals and depressive symptoms in a total of 854 patients of a 3,646-sample size. The studies mostly included those with MDD, except for 2 studies that included post-stroke depression patients and older people with depressive and anxiety symptoms. With VFT as the majority, the studies adopted varied activation tasks such as Japanese Shitori task, resting state, speech, two-back task, n-back task, standing, rumination induction, mental rotation, Stroop task, TSST, SECPT, CFT, and BACS-J. The observed depression symptoms included suicidal ideation, rumination, maladaptive coping strategy, emotional symptoms, cognitive impairment, and psychomotor retardation. All the studies with the country origin of South Korea (n = 3) focused mainly on suicidal ideation.

Many studies found a negative correlation between overall depressive symptom severity and HbO levels in frontotemporal brain areas. Significant negative correlations were revealed between HAMD scores and HbO in the TC area of MDD patients [28], between HAMD scores changes and HbO change in the right IFG in severity-dependent regions [29], and between HAMD scores and HbO integral values in the frontal lobe of PSD patients [30]. Tsujii et al. [31] investigated the neural basis of maladaptive coping strategies of remitted MDD (rMDD) for stressful situations. It was observed that rMDD achieved significantly higher avoidance-oriented coping scores compared to HCs, and that these scores were significantly and negatively associated with the hemodynamic response in their right inferior frontal gyrus.

Studies utilized rumination induction to look for an association between depressive symptoms with hemodynamic changes. It was found that social stress, which triggered hypoactivity in the Cognitive Control Network in MDD, induced depressive rumination [32]. One study evaluated the amplitude of low-frequency fluctuations (ALFF) [33]. However, during the rumination induction, though a general hypoactivity in the MDD group was observed compared to HCs, both groups showed an increased ALFF. This suggests that different paradigms need to be considered.

Studies also observed depressive and anxiety symptoms in older adults. It was found that decreased lateral PFC functioning in particular cognitive control domains is related to these symptoms [34]. One study revealed that lower baseline systolic blood pressure is associated with clinically significant depressive symptoms [35]. The study demonstrated that lower blood pressure is related to lower frontal lobe perfusion. Given the association, it may represent a potential therapeutic target for the prevention of incident depression in older people.

Studies have also focused on cognitive impairment. It was revealed that depressive adolescents exhibited an abnormal activation pattern and decreased task-related functional connectivity compared to HCs, and though the HbO changes are negatively correlated with HAMD scores, it is not sensitive to depression symptoms [36]. One study that investigated the relationship between MDD cognitive function impairment and brain activity observed a correlation between reduced activation in the left temporal region and poor motor speed in patients with MDD [37].

One study investigated the neural mechanism underlying the ability to process the mental rotation in different depressive tendency individuals with psychomotor retardation [38]. It was found that neural areas of higher-depressive-tendency-individuals rise in the frontal and motor cortex.

Some studies put efforts to find a tool that objectively assesses the risk of suicidal ideation. These studies were all conducted in South Korea in which 2 of them were concerned with suicidal ideation in young adults with MDD. It was found that executive impairment has a correlation with hemodynamic changes in young adults with MDD [39]. The executive impairment is a characteristic of suicidality in MDD. Increased suicidal ideation severity was associated with decreased HbO in the left VLPFC of young adults with MDD [40]. Prefrontal asymmetry was significantly and positively correlated with suicidal ideation in MDD [41].

Monitoring Treatment Outcome

Thirteen studies are identified utilizing fNIRS to monitor treatment responses in depressed patients. The HbO changes were specifically observed to monitor the treatment response in various type of treatments. Six studies used transcranial magnetic stimulation (either rTMS or iTBS) [42-47]. Other articles assessed electroconvulsive therapy [48], antidepressant (sertraline treatment) [49], acupuncture [50-51], antidepressants with/without acupuncture [50], music therapy [52], hypnotherapy and cognitive behavioral therapy [53], and therapeutic garden exposure [54].

The summary of studies' category-related main findings or results are presented by **Table 1**. The more detailed information for each category is provided by Table 2 to 4.

Table 1: Summary of the studies.

Category of the study	Category-related main findings/results
Differentiating depression from other disorders and healthy individuals	Differentiating MDD from HCs: • Reduced hemodynamic response in left PFC and between bilateral PFC in MDD [7]. • The ability of depressed individuals (MDD/Bipolar I/Bipolar II) to discriminate neutral and emotional facial expressions may be affected by aberrant functioning of right PFC [13]. • Reduced frontal and temporal hemodynamic response in MDD [5]. • Reduced frontotemporal hemodynamic response and reduced metabolite concentrations via amino acid profiling in MDD patients [6]. • MDD patients had aberrant functional connectivity and blood oxygenation. Negative correlation between HbO and sleep status in MDD patients [9].

	• A multimodal machine learning model demonstrated the highest diagnostic accuracy for MDD compared with a unimodal and bimodal model. The model integrated sociodemographic, clinical, and fNIRS data [24]. • Abnormalities in RSFC patterns in MDD can be partially detected using NIRS [25]. • Patterns of PFC functional connectivity differed significantly between MDD and HCs [10]. • The abnormal PFC activity of MDD may be quantified as a diminished relative intensity and inappropriate activation timing of hemodynamic response [27]. • Hypo-activated HbO in left FC to unfavorable stimuli, but no significant difference between MDD and HCs to favorable stimuli [11].
	Differentiating MDD from SCH: • SCH and MDD patients have different levels of impairment in different cognitive domains and different patterns of brain activation between VFT and TOL [15]. • NIR-TRS showed reduced anterior PFC blood volume in SCH but not in MDD and could be useful for differentiating SCH and MDD [16].
	Differentiating ASD with/without depression, & TD: • Reduced activation in the right VLPFC might indicate depression in adolescents with ASD [21]. • Reduced activation in the right VLPFC found in both ASD groups. Reduced right anterior TC activation in ASD+D compared to ASD-D and reduced left VLPFC activation compared to TD [22].
	Differentiating MDD from BD: • The association between hemodynamic response and mitochondrial dysfunction could play an important role in differentiating BD from MDD [19].
	Differentiating MDD with TRD from MDD without TRD: • Different patterns of abnormal frontal activation found between MDD patients with and without TRD [12].
	Differentiating Remitted from HCs: • PFC activation could differentiate HCs from subjects in remission from mental disorders with depressive symptoms [14].
	Differentiating MDD and/or A&D from HCs: • Non-task may not be sufficient to separate MDD or A&D from HCs [18]. • HCT created a stronger cortex activation than VFT and was more efficient in differentiating A&D patients from HCs. HbO responses were related to the progress of A&D [23].
	Differentiating MDD/BD from SCH & HCs: • A combined index of Integral Value of R1 and Centroid Value of R2 can better differentiate individuals with MDD/BD from HC than from SCH [26].
	Differentiating MDD, GAD, CMG from HCs, and MDD from GAD/CMG: • Reduced HbO in left VLPFC and DLPFC in MDD, GAD and CMG compared to HCs. Reduced HbO in FPC in MDD compared with GAD and CMG [8].
	Differentiating BD, UD, & HCs: • Hemodynamic PFC activation: HC > BD > UD. Different specific activation patterns found between UD and BD [20].
	Differentiating MDD/BPD from HCs, and MDD from BPD: • Reduced frontal, temporal and parietal hemodynamic response in BPD and MDD compared with HC. Reduced hemodynamic response in right FC in MDD patients compared with [17].
Correlating fNIRS data with depression symptoms	Patients/individuals with depressive symptoms and/or cognitive impairment: • Smaller PFC & inferior PC activation during task in MDD than in HC. A significant negative correlation between HbO in TC and HAM-D-score in MDD patients [28]. • Brain activation in the right IFG and bilateral MFG may differentially indicate clinical severity and trait-related abnormalities in MDD [29]. • Participants with depressive symptoms had lower frontal lobe perfusion than non-depressed participants [35]. • fNIRS-VFT paradigm detects changes in cortical activation and functional connectivity in adolescent-onset depression but is not sensitive to depressive symptoms [36]. • Negative correlation between HbO integral values and HAM-D scores and a significant difference in HbO integral value between PSD and non-PSD [30].
	Patients/individuals with suicidal ideation: • Reduced prefrontal activation during task in MDD compared with HCs. More prominent impairment in patients with suicidality than those without. Significant differences in left FPC [39]. • Hypofunction in left DLPFC, left VLPFC & both OFC in MDD patients. Decreased HbO in left VLPFC associated with increased suicidal ideation intensity [40]. • Reduced left PFC HbO changes during VFT in MDD compared to HCs. PFC asymmetry moderated the effect of depression severity on suicide ideation [41].
	Patients/individuals with rumination: • Social stress but not physiological stress induced rumination in MDD patients. NIRS showed hypoactivity in the cognitive control network in MDD patients during TSST [32]. • Evidence for a successful rumination induction through a direct induction paradigm; not specific to depressed subjects. General hypoactivity in MDD compared to HC [33].

	Patients/individuals with maladaptive coping strategies: • Hemodynamic changes in the right IFC were associated with dysfunctional stress response in rMDD patients. Differential functioning patterns associated with coping strategies may link to MDD recurrence vulnerability [31].
	Patients/individuals with emotional symptoms: • Depressive and anxiety symptoms are associated with decreased lateral PFC functioning in nonpsychiatric older adults [34].
	Patients/individuals with psychomotor retardation: • Areas in FC and MC connected with psychomotor retardation in depressed individuals during mental rotation [38].
	Patients/individuals with cognitive function impairment: • Reduced left TC HbO changes could be a biomarker for poor motor speed in MDD [37].
Assessing treatment response using fNIRS	With rTMS treatment: • Increased cerebral blood flow & decreased symptoms in 14/15 patients after treatment [42]. • Laterality of the PFC hemodynamic response had a significant leftward shift after treatment. Pre-treatment laterality index is a potential predictor for rTMS outcome [45]. • fNIRS-measured PFC activation during VFT is a potential biomarker for monitoring MDD patients' treatment response to rTMS [47].
	With iTBS treatment: • Cumulative treatment effect was found in the PFC blood oxygenation response related to iTBS [43]. • Combined findings from fNIRS and fMRI suggest that changes within the salience network and the central executive network affect the fNIRS response to iTBS [44]. • Active iTBS over DMPFC did not affect cognitive performance or PFC oxygenation in patients [46].
	With acupuncture and antidepressant treatment: • Increased RSFC in treatment group compared to control group [50].
	With electroconvulsive therapy treatment: • Reduced bilateral frontal HbO responses in patients compared to HC. Further reduced HbO responses after ECT but no correlation with mood or cognitive changes [48].
	With sertraline treatment: • NIRS is a potential biological marker for predicting clinical response to sertraline treatment [49].
	With acupuncture treatment: • No significant change in PFC activity in patients with mild to moderate symptoms, but increased FP activation in patients with severe symptoms [51].
	With music therapy treatment: • Music therapy could change the hemodynamics of the left DLPFC, VMPFC and OFC and improve the brain function of MDD patients [52].
	With hypnotherapy or CBT treatment: • HT affects emotional processing, and this effect is moderated by rumination [53].
	With therapeutic garden treatment: • Neurophysiological evidence for benefits of passive exposure to therapeutic nature in depressed patients and non-clinical population [54].

MDD: Major Depressive Disorder; HC: Healthy Control; PFC: Prefrontal Cortex, Hbo: Oxygenated Hemoglobin; Fnirs: Functional Near-Infrared Spectroscopy; RSFC: Resting-State Functional Connectivity; FC: Frontal Cortex; SCH: Schizophrenia; VFT: Verbal Fluency Task; TOL: Tower Of London; NIR-TRS: Near-Infrared Time-Resolved Spectroscopy; ASD: Autism Spectrum Disorder; TD: Typically Developed Controls; VLPF: Cventrolateral PFC; TC: Temporal Cortex; ASD+D: ASD With Depression; ASD-D: ASD Without Depression; BD: Bipolar Depression / Bipolar Disorder; TRD: Treatment-Resistant Depression; A&D: Anxiety & Depression; HCT: High-Level Cognition Task; GAD: Generalized Anxiety Disorder; CMG: Comorbid MDD & GAD; DLPFC = DLPFC: Dorsolateral PFC; DMPFC: Dorsomedial PFC; FPC: Frontopolar Cortex; UD: Unipolar Depression; BPD: Borderline Personality Disorder; PC: Parietal Cortex; IFG: Inferior Frontal Gyrus; MFG: Medial Frontal Gyrus; PSD: Post-Stroke Depression; OFC: Orbitofrontal Cortex (OFC); TSST: Trier Social Stress Test; Rmdd: Remitted MDD; IFC: Inferior Frontal Cortex; MC: Motor Cortex; Rtms: Repetitive Transcranial Magnetic Stimulation; Itbs: Intermittent Theta-Burst Stimulation; ECT: Electroconvulsive Therapy; Fmri: Functional Magnetic Resonance Imaging; DMPFC = ; FP: Frontopolar; VMPFC: Ventromedial Prefrontal Cortex; CBT: Cognitive Behavioral Therapy

NA: Not Available; HC: Healthy Control; D: Depressed; MDD: Major Depressive Disorder; A&D: Anxiety & Depression; SCH: Schizophrenia; GAD: Generalized Anxiety Disorder; CMG: Comorbid MDD & GAD; UD: Unipolar Depression; BD: Bipolar Depression / Bipolar Disorder; BPD: Borderline Personality Disorder; ASD: Autism Spectrum Disorder; TD: Typically Developed Controls; DSM: Diagnostic And Statistical Manual Of Mental Disorders; SCID: Structured Clinical Interview For DSM; MINI: Mini-International Neuropsychiatric Interview; HAM-D: Hamilton Rating Scale For Depression; BDI: Beck Depression Inventory; PHQ: Patient Health Questionnaire; MADRS: Montgomery Åsberg Depression Rating Scale; POMS: Profile Of Mood States; CES-D: Center For Epidemiological Studies Depression Scale; RSFC: Resting-State Functional Connectivity; FC: Frontal Cortex; PFC: Prefrontal Cortex; FPC: Frontopolar Cortex; TC: Temporal Cortex; PC: Parietal Cortex; OC: Occipital Cortex; DLPFC: Dorsolateral PFC; VLPFC: Ventrolateral PFC; DMPFC: Dorsomedial PFC; VFT: Verbal Fluency Task

Ohtani et al. (2021) [21]	Japan	ASD+D: 14 (5/9) ASD-D: (5/9) TD: 14 (4/10)	ASD+D: 22.64 ± 2.41 ASD-D: 23.07 ± 2.50 TD: 21.64 ´ 1.15	DSM-V	BDI-II	All medication-free	52-channel ETG-4000 (Hitachi)	VFT	PFC, TC	Reduced activation in the right VLPFC might indicate depression in adolescents with ASD.
Tseng et al. (2022) [12]	Taiwan	MDD: 27 (21/6) TRD: 27 (22/5) HC: 27 (21/6)	MDD: 65.3 ± 8.5 TRD: 66.5 ± 6.0 HC: 65.6 ± 7.7	DSM-V MINI) Thase and Rush staging of treatment resistance	HAM-D	All medication-free for at least 1 week	NA	Finger tapping, VFT, dual task (VFT + finger tapping)	FC	Different patterns of abnormal frontal activation found between MDD patients with and without TRD.
Manelis et al. (2019) [13]	USA	MDD/BD: 33 (23/10) HC: 20 (14/6)	MDD: 23.57 ± 5.27 HC: 25.72 ± 6.85	DSM-V (MINI)	HAM-D	23 depressed patients on psychotropic medication	CW6 fNIRS (Techen)	Emotional intensity rating task	FC	The ability of depressed individuals to discriminate neutral and emotional facial expressions may be affected by aberrant functioning of right PFC.
Li et al. (2022) [27]	Singapore	MDD: 177 (97/80) HC: 186 (111/75)	MDD: 39.0 ± 13.9 HC: 36.4 ± 14.2	DSM (SCID)	HAM-D	Some of the patients on antidepressants	52-channel fNIRS	VFT	FC, TC	The abnormal PFC activity of MDD may be quantified as a diminished relative intensity and inappropriate activation timing of hemodynamic response.
Ohtani et al. (2021) [22]	Japan	ASD+D: 12 (4/8) ASD-D: 12 (3/9) TD: 12 (3/9)	ASD+D: 22.17 ± 2.25 ASD-D: 22.67 ± 1.56 TD: 21.83 ± 0.94	DSM-V (MINI)	BDI-II	All medication-free	52-channel ETG-4000 (Hitachi)	Emotional face recognition task (EFRT)	FC, TC	↓ right VLPFC activation in both ASD groups. ↓ right anterior TC activation in ASD+D compared to ASD-D and ↓ left VLPFC activation compared to TD.
Nishizawa et al. (2019) [11]	Japan	MDD: 14 (7/7) HC: 20 (7/13)	MDD: 38.2 ± 12.9 HC: 29.0 ± 5.7	DSM-IV	HAM-D	All except four patients on antidepressants	22-channel ETG-4000 (Hitachi)	Emotional Stroop task	FC, TC	Hypo activated HbO in left FC to unfavorable stimuli, but no significant difference between MDD and HC to favorable stimuli.
Tsujii et al. (2019) [19]	Japan	MDD: 44 (13/31) BD: 79 (39/40) HC: 58 (29/29)	MDD: 42.9 ± 10.8 BD: 43.4 ± 12.4 HC: 48.2 ± 13.1	DSM-IV or DSM-V	HAM-D	Many patients on antidepressants, antipsychotics or mood stabilizers	52-channel ETG-4000 (Hitachi)	VFT	PFC, TC	The association between hemodynamic response and mitochondrial dysfunction could play an important role in differentiating BD from MDD.
Atsumori et al. (2019) [14]	Japan	Remitted: 21 (5/16) HC: 29 (12/17)	Remitted: 40.9 ± 6.31 HC: 35.9 ± 7.7	NA	POMS	NA	ETG-4000 (Hitachi) for HC and a wearable optical topography prototype (Hitachi) for D	Working memory tasks	PFC	PFC activation could differentiate healthy controls from subjects in remission from mental disorders with depressive symptoms.
Lang et al. (2021) [23]	China	A&D acute stage: 10 A&D consolidation: 10 A&D maintenance: 10 HC: 10	A&D acute: 60.4 ± 18 A&D consolidation: 57.5 ± 10.3 A&D maintenance: 61.6 ± 17.9 HC: 32.1 ± 10.6	DSM-V	HAM-D	NA	52-channel ETG-4000 (Hitachi)	VFT, HCT (high-level cognition task)	PFC, TC	HCT created a stronger cortex activation than VFT and was more efficient in differentiating A&D patients from HC. HbO responses were related to the progress of A&D.
Xiang et al. (2021) [15]	China	MDD: 30 (18/12) SCH: 30 (16/14) HC: 30 (18/12)	MDD: 29.40 ± 8.87 SCH: 27.23 ± 7.04 HC: 27.27 ± 7.90	DSM-V	HAM-D	All patients on medications	32-channel CW5 (TechEn)	VFT, TOL (Tower of London)	PFC	SCH and MDD patients have different levels of impairment in different cognitive domains and different patterns of brain activation between VFT and TOL.
Shinba et al. (2022) [16]	Japan	MDD: 15 (8/7) SCH: 12 (6/6) HC: 15 (9/6)	MDD: 39.1 ± 8.9 SCH: 39.6 ± 13.4 HC: 37.9 ± 12.0	DSM-V	NA	All patients on antipsychotics (SCH) or antidepressants (MDD)	Single-channel TRS-10 (Hamamatsu)	Resting state	FC	NIR-TRS showed ↓ anterior PFC blood volume in SCH but not in MDD and could be useful for differentiating SCH and MDD.

Table 2: Summary of the studies differentiating depression from other disorders and healthy individuals.

Study	Country	Sample size (female/male)	Age (mean ± standard deviation)	Diagnostic criteria	Psychopathology measure for depression	Medication	NIRS device	Activation tasks	Brain area	Main findings
Wen et al. (2021) [18]	China	MDD: 10 A&D: 10 HC: 10	MDD: 29.8 ± 11.8 A&D: 30.0± 11.4 HC: 31.8 ± 11.1	DSM-V	NA	NA	52-channel ETG4100 (Hitachi)	non-task and VFT	PFC, TC	Non-task may not be sufficient to separate MDD or A&D from HC.
Wei et al. (2021) [26]	China	MDD: 54, (29/25), SCH: 198 (121/77) BD: 64 (44/20) HC: 101 (64/37)	MDD: 34.06 ± 12.70 SCH: 38.19 ± 12.66 BP: 34 ± 12,66 HC: 27.55 ± 6.35	DSM-IV, ICD-10	HAM-D	NA	52-channel ETG4000 (Hitachi)	VFT	PFC, TC	A combined index of Integral Value of R1 and Centroid Value of R2 can better differentiate individuals with MDD/BD from HC than from SCH.
Husain et al. (2020) [5]	Singapore	MDD: 105 (60/45) HC: 105 (65/40)	MDD: 36.2 ± 13 HC: 36.4 ± 13	DSM-V	HAM-D	Majority of patients on antidepressants, a fraction on anxiolytics or antipsychotics	52-channel ETG-4000 (Hitachi)	VFT	PFC, FPC, TC	↓ frontal and temporal hemodynamic response in MDD.
Hu et al. (2021) [8]	China	MDD: 52 (37/15) GAD: 51 (12/39) CMG: 52 (26/26) HC: 47 (26/21)	MDD: 40.27 ± 13.79 GAD: 42.57 ± 11.68 CMG: 41.27 ± 12.09 HC: 36.06 ± 10.40	DSM-V	HAM-D	MDD: 20, GAD: 12, CMG: 26 patients on medication	45-channel Foire-3000 (Shimadzu)	VFT	PFC	↓ HbO in left VLPFC and DLPFC in MDD, GAD and CMG compared to HC. ↓ HbO in FPC in MDD compared with GAD and CMG.
Feng et al. (2021) [20]	China	UD: 69 (42/27) BD: 68 (38/30) HC: 42 (21/21)	UD: 23.90 ± 9.16 BD: 30.66 ± 11.29 HC: 28.36 ± 8.21	DSM-V	HAM-D, MINI	NA	45-channel Foire-3000 (Shimadzu)	VFT	PFC	Hemodynamic PFC activation: HC > BD > UD. Different specific activation patterns between UD and BD.
Ong et al. (2021) [6]	Singapore	MDD: 25 (18/7) HC: 25 (18/7)	MDD: 29.5 ± 8.7 HC: 30.3 ± 8.6	DSM-V	HAM-D	MDD: 17 patients on medication	52-channel ETG4000 (Hitachi)	VFT	FC, TC	↓ frontotemporal hemodynamic response and ↓ metabolite concentrations via amino acid profiling in MDD patients.
Chao et al. (2021) [9]	China	MDD: 16 (12/4) HC: 16 (10/6)	MDD: 35.5 ± 9.0 HC: 36.2 ± 11.7	NA	PHQ-9, PHQ-15	NA	22-channel CW NIRScout (NIRx Medical Technologies)	Sound stimuli paradigm, resting state	PFC	MDD patients had aberrant functional connectivity and blood oxygenation compared with HC. Negative correlation between HbO and sleep status in MDD patients.
Husain et al. (2020) [17]	Singapore	MDD: 31 BPD: 31 HC: 31 all female	MDD: 31.8 ± 10.1 BPD: 31.8 ± 10.2 HC: 31.7 ± 10.5	DSM-V (SCI)	HAM-D	MDD: 22 & BPD: 26 on medication (mainly antidepressants, but. a few also anxiolytics, sedatives or mood stabilizers)	52-channel ETG4000 (Hitachi)	VFT	PFC, FPC, TC	↓ frontal, temporal and parietal hemodynamic response in BPD and MDD compared with HC. ↓ hemodynamic response in right FC in MDD patients compared with BPD.
Gao et al. (2019) [7]	China	MDD: 27 (20/7) HC: 24 (13/11)	MDD: 40.78 ± 13.42 HC: 43.13 ± 11.28	DSM-IV	HAM-D	All medication-free for at least 4 weeks	CW-NIRS	Facial recognition	PFC	↓ hemodynamic response in left PFC and between bilateral PFC in patients compared with HC.
Ho et al. (2022) [24]	Singapore	MDD: 65 (49/16) HC: 68 (53/15)	MDD: 28.3 ± 7.2 HC: 28.3 ± 7.3	DSM-V	HAM-D	56 MDD patients on medication	52-channel ETG-4000 (Hitachi)	VFT	PFC	A multimodal machine learning model demonstrated the highest diagnostic accuracy for MDD compared with a unimodal and bimodal model.
Sakakibara et al. (2021) [25]	Japan	MDD: 34 (17/17) HC: 78 (42/36)	MDD: 37.4 ± 9.9 HC: 37.3 ± 7.2	DSM-IV	CES-D, HAM-D	A high percentage of the patients on antipsychotics and mood stabilizers	ETG-4000 (Hitachi)	Resting state	FC, TC, PC, OC	Abnormalities in RSFC patterns in MDD can be partially detected using NIRS.
Dong et al. (2021) [10]	South Korea	MDD: 31 HC: 43	MDD: 39.48 ± 13.82 HC: 34.26 ± 12.47	DSM-V	HAM-D, BDI-II	NA	48-channel NIRSIT (OBELAB)	VFT	PFC	Patterns of PFC functional connectivity differed significantly between MDD and HC.

Table 3: Summary of the studies correlating fNIRS data with depression symptoms.

Study	Country	Sample size (gender)	Age (mean ± standard deviation)	Diagnostic criteria	Psychopathology measure	Specific symptoms	NIRS device	Activation tasks	Brain area	Main findings
Ishii et al. (2021) [28]	Japan	MDD: 29 (11/18) HC: 29 (13/16)	MDD: 34.1 ± 7.8 HC: 31.0 ± 6.2	ICD-10	HAM-D	Depressive symptoms	44-channel ETG-4000 (Hitachi)	Japanese shiritori task	FC, TC, PC	Smaller PFC & inferior PC activation during task in MDD than in HC. A significant negative correlation between HbO in TC and HAM-D-score in MDD patients.
Kim et al. (2022) [39]	South Korea	MDD: 35 (8/27) without and 25 (9/25) with suicidality HC: 59 (32/27)	MDD without: 24.26 ± 4.46 MDD with: 24.43 ± 4.74 HC: 27.83 (3.48)	DSM-V, MINI	HAM-D	Suicidality	48-channel NIRSIT (OBELAB)	Resting state, speech, VFT	PFC	↓ prefrontal activation during task in MDD compared with HC. More prominent impairment in patients with suicidality than those without. Significant differences in left FPC.
Lee et al. (2021) [40]	South Korea	MDD: 45 (27/18) HC: 32 (23/9)	MDD: 28.24 ± 4.40 HC: 28.78 ± 3.27	DSM-V	BDI-II, SSI-BECK	Suicidal ideation	48-channel NIRSIT (OBELAB)	VFT	PFC	Hypofunction in left DLPFC, left VLPFC & both OFC in MDD patients. ↓ HbO in left VLPFC associated with ↑suicidal ideation intensity.
Rosenbaum et al. (2021) [32]	Germany	MDD: 22 HC: 23	MDD: 27.14 ± 6.15) HC: 25.35 ± 5.75	NA	BDI-II	Rumination	multi-channel ETG-4000 (Hitachi)	TSST, SECPT	PFC, IFG, SFL	Social stress but not physiological stress induced rumination in MDD patients. NIRS showed hypoactivity in the cognitive control network in MDD patients during TSST.
Satomura et al. (2019) [29]	Japan	MDD Initially: 165 After 1.5 years: 45	39.8 ± 11.8	DSM-IV	HAM-D	Depressive symptoms	52-channel ETG-4000 (Hitachi)	VFT	PFC, T	Brain activation in the right IFG and bilateral MFG may differentially indicate clinical severity and trait-related abnormalities in MDD.
Tsujii et al. (2021) [31]	Japan	remitted MDD: 45 (20/25) HC: 56 (25/31)	rMDD: 43.2 ± 13.3 HC: 40.9 ± 12.7	DSM-IV, MINI	HAM-D	Maladaptive coping strategies	52-channel ETG4000 (Hitachi)	VFT	PFC, TC	Hemodynamic changes in the right IFC were associated with dysfunctional stress response in rMDD patients. Differential functioning patterns associated with coping strategies may link to MDD recurrence vulnerability.
Yeung et al. (2021) [34]	China	36 (23/13)	62.6 ± 7.5	NA	CGDS-15	Emotional symptoms	16-channel OEG-SpO2 (Spectratech)	n-back task, CFT	PFC	Depressive and anxiety symptoms are associated with decreased lateral PFC functioning in nonpsychiatric older adults.
Briggs et al. (2019) [35]	Ireland	D: 209 (129/80) HC: 2407 (1282/1125)	D: 64.5 HC: 63.5	NA	CES-D	Depressive symptoms	Artinis Portalite System CW-NIRS	standing	FC	Participants with depressive symptoms had lower frontal lobe perfusion than non-depressed participants.
Liu et al. (2022) [36]	China	MDD: 72 (58/14) HC: 74 (54/20)	MDD: 14.29 ± 1.34 HC: 15.54 ± 1.46	DSM-V	HAM-D	Depressive symptoms, cognitive impairment	48-channel NirScan	VFT	PFC, TC	fNIRS-VFT paradigm detects changes in cortical activation and functional connectivity in adolescent-onset depression but is not sensitive to depressive symptoms.
Rosenbaum et al. (2020) [33]	Germany	MDD: 26 (17/9) HC: 26 (21/5)	MDD: 41.85 ± 11.70 HC: 35.65 ± 13.25	DSM-IV	BDI-II, MADRS	Rumination	Multichannel ETG-4000 (Hitachi)	Rumination induction	FC, PC, TC	Evidence for a successful rumination induction through a direct induction paradigm; not specific to depressed subjects. General hypoactivity in MDD compared to HC.
Wang et al. (2022) [38]	China	Lower depressive tendency: 27 Higher depressive tendency:13	NA	NA	BDI-II	Psychomotor retardation	20-channel LABNIRS (Shimadzu)	Mental rotation	FC	Areas in FC and MC connected with psychomotor retardation in depressed individuals during mental rotation.
Baik et al. (2019) [41]	South Korea	MDD: 42 (34/17) HC: 64	MDD: 37.62 ± 14.36 HC: 33.42 ± 12.57	DSM-V	BDI-II, HAM-D	Suicidal ideation	48-channel NIRSIT (OBELAB)	VFT, Stroop task, two-back task	PFC	↓ left PFC HbO changes during VFT in MDD compared to HC. PFC asymmetry moderated the effect of depression severity on suicide ideation.

Kiriyama et al. (2020) [37]	Japan	MDD: 18 (6/12) HC: 22 (11/11)	MDD: 44.2 ± 8.9 HC: 42.0 ± 11.2	DSM-V	HAM-D	Cognitive function impairment	52-channel ETG-4000 (Hitachi)	BACS-J	FC, TC	↓ left TC HbO changes could be a biomarker for poor motor speed in MDD.
Koyanagi et al. (2021) [30]	Japan	PSD: 13 (4/9) non-PSD: 32 (9/23)	67.8 ± 12.9	NA	HAM-D	Depressive symptoms in PSD	46-channel OMM-3000/16 (Shimadzu)	VFT	FC, TC	Negative correlation between HbO integral values and HAM-D scores and a significant difference in HbO integral value between PSD and non-PSD.

NA: Not Available; MDD: Major Depressive Disorder, PSD: Post-Stroke Depression; Rmdd: Remitted MDD; DSM: Diagnostic And Statistical Manual Of Mental Disorders; MINI: Mini-International Neuropsychiatric Interview; ICD: International Classification Of Diseases; HAM-D: Hamilton Rating Scale For Depression; BDI: Beck Depression Inventory; SSI-BECK: Beck Scale For Suicidal Ideation; MADRS: Montgomery Åsberg Depression Rating Scale; POMS: Profile Of Mood States; CGDS: Chinese Geriatric Depression Scale; RSFC: Resting-State Functional Connectivity; FC: Frontal Cortex; PFC: Prefrontal Cortex; TC: Temporal Cortex; PC: Parietal Cortex; DLPFC: Dorsolateral PFC; VLPFC: Ventrolateral PFC; IFG: Inferior Frontal Gyrus; MFG: Medial Frontal Gyrus; VFT: Verbal Fluency Task; TSST: Trier Social Stress Test; SECPT: Socially Evaluated Cold-Pressor Test; CGDS-15: Chinese Geriatric Depression Scale; CES-D: Center For Epidemiologic Studies Depression Scale; CFT: Category Fluency Task

Table 4: Summary of the studies assessing treatment response.

Study	Country	Sample size (female/male)	Age (mean ± standard deviation)	Diagnostic criteria	Psychopathology measure for treatment response	Medication or treatment	Duration	NIRS specifics	Activation tasks	Brain area	Main findings
Kawabata et al. (2022) [42]	Japan	MDD: 15 (8/7)	42.87 ± 8.93	DSM-iV (SCID)	HAM-D	rTMS	6 weeks, 5 days a week	15-channel OEG-17ME (Spectratech)	VFT	FC, TC	↑ cerebral blood flow & ↓ symptoms in 14/15 patients after treatment.
Wong et al. (2021) [50]	China	Treatment: 50 (34/16) Control: 20 (14/6)	49.2 ± 11.2	DSM-V	HAM-D, PHQ-9	Treatment: acupuncture + antidepressant Control: antidepressants	3 weeks, 2 times a week	18-channel NIRSport	Supine resting state	DLPFC	↑ RSFC in treatment group compared to control group.
Downey et al. (2019) [48]	UK	UD/BD: 18 (8/10) HC: 51 (30/21)	UD/BD: 56.2 ± 12.1 HC: 51.6 ± 15.6	DSM-IV (MINI)	MADRS	ECT (12 patients); all patients on ketamine	4 treatments	24-channel NTS optical imaging system (Gowerlabs)	VFT , N-Back working memory task	PFC	↓ bilateral frontal HbO responses in patients compared to HC. Further ↓ HbO responses after ECT but no correlation with mood or cognitive changes.
Struckmann et al. (2021) [43]	Sweden	UD: 36 and BD: 4 of which Active iTBS: 18 (10/8) Sham: 21 (11/10)	Active: 30 ± 11 Sham: 29 ± 9	MINI	MADRS	iTBS	twice a day for 10-15 consecutive working days	2-channel NIRO-200NX (Hamamatsu)	During iTBS stimulation (event-related) and resting state	PFC	Cumulative treatment effect was found in the PFC blood oxygenation response related to iTBS.
Struckmann et al. (2022) [44]	Sweden	Active: 17 (9/8) Sham: 17 (9/8)	Active: 30.9 ± 10.3 Sham: 27.1 ± 7.2	MINI	MADRS, CAINS, BPRS, MSM	iTBS	10 days, twice a day	2-channel NIRO 200X (Hamamatsu)	During iTBS stimulation	PFC	Combined findings from fNIRS and fMRI suggest that changes within the salience network and the central executive network affect the fNIRS response to iTBS.
Yamagata et al. (2019) [49]	Japan	MDD: 11 (6/5)	36.3 ± 11.2	DSM-IV	HAM-D	Antidepressant (sertraline)	12 weeks, measurements every 4 weeks	52-channel ETG-4000 (Hitachi)	VFT	FC, TC	NIRS is a potential biological marker for predicting clinical response to sertraline treatment.
Zhang et al. (2021) [51]	China	MDD: 47 (37/10)	39.70 ± 12.24	DSM-IV	HAM-D	Acupuncture	one single session	52-channel ETG-4100 (Hitachi)	VFT	PFC	No significant change in PFC activity in patients with mild to moderate symptoms, but ↑ FP activation in patients with severe symptoms.

Feng et al. (2019) [52]	China	MDD: 15 (8/7) HC: 15 (9/6)	MDD: 30.93 ± 13.47 HC: 30.87 ± 10.11	DSM-V	HAM-D	Music therapy	10 days, one 1h session a day	45-channel FOIRE-3000 (Shimadzu)	VFT	PFC	Music therapy could change the hemodynamics of the left DLPFC, VMPFC and OFC and improve the brain function of MDD patients.
Yamazaki et al. (2022) [45]	Japan	MDD: 19 (7/12)	48.6 ± 12.2	DSM-V	MADRS	rTMS	maximum 6 weeks, once daily for up to 5 days a.week	16-channel Spectratech OEG-16	VFT	PFC	Laterality of the PFC hemodynamic response had a significant leftward shift after treatment. Pre-treatment laterality index is a potential predictor for rTMS outcome.
Haipt et al. (2022) [53]	Germany	MDD: 75 (56/19) of which CBT: 39 HT: 36	39.24 ± 14.85	DSM-IV	NA	Hypnotherapy (HT) vs. cognitive behavioral therapy	20 weeks, 16-20 sessions in total	52-channel ETG-4000 (Hitachi)	Emotional gait paradigm	OC, TC	HT affects emotional processing, and this effect is moderated by rumination.
Struckmann et al. (2021) [46]	Sweden	Active: 25 (14/11) Sham: 26 (14/12) HC: 55 (37/18)	Active: 30.04 ± 9.84 Sham: 29.04 ± 8.73 HC: 30.20 (10.55)	MINI	CAINS, MSM, BPRS, MADRS	iTBS	10 days, twice a day	2-channel NIRO-200 NX (Hamamatsu)	Trail making test, RAVLT, animal naming test, digit symbol coding test, Sternberg memory test, emotional Stroop test, Corsi block tapping test	PFC	Active iTBS over DMPFC did not affect cognitive performance or PFC oxygenation in patients.
Olzewska-Guizzo et al. (2022) [54]	Singapore	MDD: 24 (15/9) HC: 68 (37/31)	MDD: 31 ± 9.59 HC: 38.79 ± 17.01	NA	BDI-II	therapeutic garden	3 sessions in 3 different locations; 30-45 min / session	NIRS SPORT (NIRx)	Passively viewing different landscapes	FC, OC	Neurophysiological evidence for benefits of passive exposure to therapeutic nature in depressed patients and non-clinical population.
Huang et al. (2022) [47]	China	MDD: 40 (32/8) HC: 40 (29/11)	MDD: 38.18 ± 9.81 HC: 37.75 ± 4.72	DSM-V	HAM-D	rTMS	4 weeks, 5 days a week	37-channel BS-3000 (Wuhan Union Medical Technology)	VFT	PFC	fNIRS-measured PFC activation during VFT is a potential biomarker for monitoring MDD patients' treatment response to rTMS.

NA: Not Available; MDD: Major Depressive Disorder; TRD: Treatment-Resistant Depression; DSM: Diagnostic And Statistical Manual Of Mental Disorders; MINI: Mini-International Neuropsychiatric Interview; ICD: International Classification Of Diseases; HAM-D: Hamilton Rating Scale For Depression; BDI: Beck Depression Inventory; SSI-BECK: Beck Scale For Suicidal Ideation; MADRS: Montgomery Åsberg Depression Rating Scale; PHQ: Patient Health Questionnaire; CAINS: Clinical Assessment Interview For Negative Symptoms; BPRS: Brief Psychiatric Rating Scale; MSM: Maudsley Staging Method For Treatment Resistant Depression; Rtms: Repetitive Transcranial Magnetic Stimulation; itb: Intermittent Theta-Burst Stiumulation; ECT: Electroconvulsive Therapy; FC: Frontal Cortex; PFC: Prefrontal Cortex; TC: Temporal Cortex; PC: Parietal Cortex; DLPFC: Dorsolateral PFC; VLPFC: Ventrolateral PFC; IFG: Inferior Frontal Gyrus; MFG: Medial Frontal Gyrus; VFT: Verbal Fluency Task; RAVLT: Rey Auditory Verbal Learning Test.

Discussion

Limitations

This work limits the search to only the PubMed database as the source. The other non-English studies on fNIRS are available. This study did not review on specificity and accuracy aspect of fNIRS data for diagnosing individuals with MDD. This study did not as well assess the quality of the included papers to assess the risk of bias.

Conclusions

The fNIRS data shows consistency in diagnosing depressed individuals when compared to the HCs. Across the studies, generally the specificity of the hemodynamic changes of depressed individuals was found the left prefrontal cortex. The fNIRS data also show to be a potential biomarker in differentiating depression from other disorders.

A negative correlation between overall depressive symptom severity and HbO levels in frontotemporal brain areas was found in many of the studies. More prominent prefrontal hy-

poactivity was associated with suicidality in a few studies. A couple of studies found that alternated hemodynamic response in left frontal or temporal cortical areas might be connected to psychomotor retardation or poor motor speed in depressed individuals.

The HbO changes were specifically observed to monitor the treatment response in various type of treatments such as transcranial magnetic stimulation (either rTMS or iTBS), electroconvulsive therapy, antidepressant (sertraline treatment), acupuncture, antidepressants with/without acupuncture, music therapy, hypnotherapy, cognitive behavioral therapy, and therapeutic garden exposure. The fNIRS signals is a potential biomarker for assessing the treatment outcome.

Acknowledgement

This study was funded by Academy of Finland Profi6 funding, 6G-Future Sustainable Society (University of Oulu), which is greatly acknowledged.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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