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REVIEW

Research progress of functional near-infrared spectroscopy in patients with psychiatric disorders

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ABSTRACT

Functional near-infrared spectroscopy (fNIRS) is a technique of detecting cerebral cortical function by using near-infrared light, which is a multifunctional neuroimaging technique and provides a convenient and efficient detection method in neuroscience. In consideration of acceptability, safety, high spatial and temporal resolutions compared with electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI), fNIRS is widely used to study different psychiatric disorders, most prominently affective disorders, schizophrenic illnesses, brain organic mental disorders and neurodevelopmental disorders, etc. The article focuses on the latest research progress and practical application of fNIRS in psychiatric disorders, especially traumatic brain, including studies on the characterization of phenomenology, treatment effects and descriptions of neuroimaging data.

Introduction

Psychiatric disorders have become a complex social and public health problem and create a new consensus on a global scale. According to relevant data [1], the rates of psychiatric illness are very high. The various psychiatric disorders will become more prominent after the 21st century. In the prediction of diseases in 2020, severe psychiatric diseases rank first in the total burden. For a long time, patients with psychiatric disorders face more physical, psychological, social and economic pressure than other patients, which brings serious economic burden and hidden danger to patients' families and society. At present, most neuropsychiatric diseases are diagnosed depending only on their clinical symptoms, lacking objective neuroimaging biomarkers. It cannot provide individual-level diagnosis and prediction, and its clinical application value is very limited [2].

Functional near-infrared spectroscopy (fNIRS) is a relatively new technology and can provide a real-time understanding of the brain function state. Ehlis et al. [3] had concluded there were at least 115 original studies that had employed fNIRS to investigate psychiatric research questions in 2014. It is a portable, inexpensive and user-friendly device which is easily adapted to the outpatient setting for the assessment of cognitive functions, which other functional imaging technologies are not. Its loose applicability and high ecological validity make fNIRS particularly suitable for psychiatric patients who may fear stressful

environments (e.g. in magnetic resonance imaging/position emission tomography (MRI/PET) scanners) or display motor restlessness (e.g. in attention deficit/hyperactivity disorder (ADHD)) by interfering with motion sensing such as MRI methods, electroencephalogram (EEG), magnetoencephalogram (MEG) or PET. Meanwhile, it has higher spatial and higher temporal resolutions in functional brain imaging than EEG and functional magnetic resonance imaging (fMRI), respectively, thus can make up for the shortcomings and interpret the research objectives more comprehensively [4]. Most of researches combine fNIRS with other brain imaging methods, such as Doppler sonography [5,6], fMRI [7–17], EEG [7,8,15–17], PET [18], and single photon emission computed tomography (SPECT), led to an amazing increase in studies implementing simultaneous applications. Despite some remaining shortcomings, including being easy to be affected by extracranial signals and anatomical parameters, fNIRS exhibits a number of important advantages making its application attractive for both neuroscience in general and psychiatric research particularly [19]. Thus, combining different imaging techniques, fNIRS can make an important contribution to the overall understanding of the functional characteristics underlying psychiatric disorders. On the other hand, fNIRS is able to assess cortical hemodynamics in the event that other methods fail (e.g. when there is a high requirement for whole-body movement in the

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subject). In summary, the advantages of fNIRS in psychiatric disorders are not only due to its relative insensitivity to movement artifacts, but also further related to its ease of use and high generality. Due to frequently repeated measurements, fNIRS can be easily used in longitudinal studies, which is becoming increasingly important in investigating the development and treatment of mental disorders.

Basic principles and advantages of fNIRS

The fNIRS is a multifunctional neuroimaging technique that uses near-infrared light to detect cerebral cortical function [20]. Near-infrared light has strong penetrability to organisms. Main substances that absorb light are oxygenated haemoglobin (HbO) and deoxygenated haemoglobin (HbR), with different absorption rates in specific bands (about 760 nm and around 850 nm) in the spectral window (600 – 900 nm).

In the active cortical region, the concentration of HbO in the haemoglobin is increased and that of HbR is decreased [21]. According to this characteristic, near-infrared light can be directly irradiated to the surface of the scalp, and the intensity of scattered light in the cerebral cortex can be measured and utilized. Using Beer-Lambert law, one can complete the conversion of raw optical data to blood oxygen concentration to achieve simultaneous multi-point measurement of HbO and HbR concentration changes in specific regions and infer the changes in blood oxygen and blood volume in this brain region. Therefore, it is possible to locate and measure the functional activation of the local cerebral cortex and to study the functional connectivity of the brain by using fNIRS.

The fNIRS was first used in animal cerebral cortex blood oxygen level testing in 1977 [3,4], and then it received extensive attention in the biomedical community. In the early stages of the study, it is only used in the study of animal or infant cerebral cortical functional activities [22]. After 1991, thanks to the development of electronic computer and optical theory, it could be used to determine the motion law and distribution of light in tissues accurately [23]. In this way, it is possible to apply near-infrared imaging technology for the detection of brain function in adults. For the mysterious organ of the human brain, the introduction of fNIRS has created new opportunities for studying the neural processes in the human cerebral cortex [19].

Schizophrenia and schizophrenia-like illness with fNIRS

The first study of fNIRS was published in 1994 of patients with schizophrenia (SZ). A split-personality questionnaire (SPQ) was used to examine the relationship between split-personality traits in non-clinical female groups with prefrontal activation patterns in the verbal fluency task (VFT) [24]. Compared with healthy subjects, the frontal lobe haemodynamic response was slower in schizophrenics with a steeper (slope) HbO concentration at the start of the task [25]. In addition, fNIRS tested brain activity in patients with SZ during a go/no-go mission, as well as their behaviour performance, was shown. It was found that SZ patients had a lower degree of activation on the frontal and temporal regions. Patients with SZ showed less activation in the superior and orbital frontal and middle temporal regions during the emotional go/no-go block [26]. Knowing the interaction between inhibition, the results indicated that frontotemporal dysfunction was associated with the pathophysiology of emotional-cognitive disorders in SZ patients [24,25,27]. Overall, these studies were performed during various neurocognitive tasks (e.g. random number generation, Hanoi Tower, Stroop, language fluency testing, go/no-go tasks). The abnormal brain activation patterns in patients with SZ were detected, especially in the prefrontal cortex (PFC) [28]. In almost all cases, reduced haemodynamic responses were observed in the frontal region of SZ patients compared with the control group [29], even when the sample's age, sex and pre-disease IQ were statistically consistent with other neuroimaging methods for the detection of cerebral ischemia [30]. In addition to these studies on different executive functions, studies have consistently demonstrated the forehead defects of the SZ patients [31].

Depressive disorders and bipolar disorders with fNIRS

Regarding the study of fNIRS in affective disorders, Okada et al. [32] conducted the first study (1996) focusing on the frontal lobe of patients with major depressive disorders (MDD) during the mirroring task. After this early work, frontal lobe abnormalities in depression were repeatedly mentioned in many fNIRS studies. Then more studies reported a reduction in bilateral anterior and posterior oxygenation times in patients with depression during the VFT [33–35]. Even more amazing is the study of healthy subjects in different emotional states, during the oral working memory (WM) task [36] or the N-Back task [37], where the relative concentration of oxyhaemoglobin in the prefrontal lobe was reported to be increased. Also, studies have also discussed the effects of some treatments on patients within prefrontal functions [36,38,39]. In addition, in 2000, researcher began to use fNIRS to study the clinical effects of repeated transcranial magnetic

stimulation (rTMS) in the left dorsal lateral pre-frontal cortex (DLPFC) of MDD patients [26].

The fNIRS has also been used to study bipolar disorder. In the resting time of WM tasks, compared with health controls, patients exhibited significantly reduced intra-regional and symmetrically interhemispheric connectivity in the PFC and decreased activity in the forehead, which could be the central neuroimaging markers of bipolar disorder [40]. But during the tasks related to attention and nonverbal cognition, on the contrary, the results showed an increase in ventral lateral dorsolateral prefrontal and frontal cortex activity in subjects and spatial visual WM storage [41]. We speculate that it may be the differences in cognitive tasks that lead to the different results. It may be that the tasks involve a wide range of prefrontal areas, and the differences in the areas of interest in the study cannot cover all of them. Of course, these findings suggest that fNIRS has the potential advantage of higher temporal resolution and can be used to investigate patients with different affective disorders, which may provide new opportunities for diagnosis.

Other mental disorders with fNIRS

The fNIRS study on anxiety has so far focused on panic disorder and dental phobia. The fNIRS studies of panic disorder have shown that the activation of left PFC is reduced during general cognitive activation [42]. The patients with panic disorder showed hypofrontality including the DLPFC via fNIRS, and verum intermittent theta burst stimulation (iTBS) could not augment prefrontal activity, nevertheless, the increased activation in the left inferior frontal gyrus has been found after sham iTBS [43]. In a large sample of 109 panic patients, task-related oxygenation can be further demonstrated. In most cases, the significant correlation between change and severity of symptoms has been shown, demonstrating that left forehead HbO is inversely related to panic attack frequency while the right forehead HbO is associated with severity of phobia [44,45].

Patients with post-traumatic stress disorder (PTSD) showed a significantly smaller response of HbO and total hemoglobin in the verbal fluency task compared with health controls via fNIRS and had significantly lower attention and concentration scores in the Wechsler Memory Scale-Revised, which was positively correlated with the increase of total hemoglobin in the verbal fluency task. Pre-frontal dysfunction in patients with PTSD may be a secondary phenomenon in reducing attention [46]. In summary, these studies have shown that PTSD patients exhibit significant cerebral haemodynamic changes in the face of trauma-related substances, and the frontal dysfunction during the cognitive tasks generally seems to be the inevitable result of the major changes in attention [47].

For one of the most frequent personality disorders, studies investigated frontal lobe function and social exclusion experience related to mood regulation. Patients with a social anxiety disorder (SAD) experienced abnormal fear in normal social situations. The result showed that the left frontal cortex was active in SAD patients [44]. In addition, when studying borderline personality disorder (BPD) while viewing sad picture data, it was found that BPD patients had a reduced slope associated with task-related increases in the left prefrontal channel compared to controls [48]. On the contrary, in the experience of social exclusion, it was found that BPD patients showed increased activation in the frontal-polar cortex [49], indicating that different neural mechanisms are the basis of different symptom dimensions. Certain personality traits have been shown to be associated with changes in cortical HbO concentration.

In the fNIRS study on addiction, Schecklmann et al. [50] studied three patient groups (acute withdrawal, detoxification and moderation) during the VFT and found generally reduced cerebral oxygenation levels in the frontotemporal region. From alcohol dependence to abstinence to normal function, during Iowa Gambling Test (IGT), Wisconsin Card Sorting Test (WCST) and N-Back, the performance of multi-substance users was worse than that of the individually matched control group. During the IGT process, they also showed less dorsolateral prefrontal oxidative. The results showed that cognitive decline was observed even after controlling for impulsivity in college students who took multiple drugs. This confirms the suitability of fNIRS to study treatment effects in both longitudinal and acute challenge environments.

Neurodevelopmental disorders with fNIRS

ADHD is a neurodevelopmental disorder prevalent in children. Neuroimaging studies have revealed neurological abnormalities in some areas of the brain, including the frontal cortex, striatum, cerebellum and occipital cortex. One study used permutation entropy (PE) to measure fNIRS in the complexity of WM task signals in children with ADHD and found that the PE value of the right dorsolateral PFC was positively correlated with the ADHD index [51]. These results suggest that the complexity analysis of fNIRS signal may be a promising tool for the diagnosis of children with ADHD. In addition, an fNIRS study recently explored the neurocognitive effects of methylphenidate (MPH) in children with ADHD during the attentional task and behavioural control paradigm [52].

In addition, autism spectrum disorder (ASD) constitutes another developmental pathology that has been frequently studied using fNIRS in the past few years. Most of these investigations are directed to prefrontal haemodynamics, which are studied in letter fluency testing. Children with ASD had a decrease in leftward bias of the balance between right and left rostral prefrontal cortex (RoPFC) activity when compared with normally developing children via fNIRS [53]. In addition, the test was also performed in the unaffected siblings of participants with ASDs. The results of the assessment suggest a change in age-related prefrontal lobe activity in ASD and the effect of genes on this phenomenon [54].

Traumatic brain injury and organic mental disorders with fNIRS

Traumatic brain injury is common in human beings. The disease can be discriminated by comparing the absorption of brain tissue on both sides. A large number of studies have also confirmed the clinical application values of fNIRS in the diagnosis and dynamic monitoring of cerebral ischemia and haemorrhagic diseases [55]. fNIRS has been used to evaluate the neurological changes in individuals with traumatic brain injury (TBI) during Stroop tasks [56,57]. The results showed that fNIRS could identify the common frontal lobe inefficiencies in TBI [58] that were the same as using fMRI [59]. Also, there is a study on the cortical activation and connectivity patterns in visual attention processing after TBI in adolescents. Focusing on the sports-related young adult concussion (SRC), the results showed that SRC group had significantly increased brain activity in the left medial frontal gyrus (MFG) and enhanced functional connectivity between the right suboccipital cortex and bilateral Calgary gyrus (CG). Interestingly, it was also found that the amount of MFG activation on the left side was significantly negatively correlated with the severity of hyperactive/impulsive symptoms in the normal control group, but not related to the patient [60]. However, in most training tasks, the change of oxyhaemoglobin in patients with TBI tends to be higher than that in the medial frontal area, and the change of oxyhaemoglobin in the two tasks in the medial frontal area is significantly different. This suggests that fNIRS measurements are also useful in assessing changes in neural activity during rehabilitation tasks in patients with TBI [61]. In a word, in studies of TBI, almost all of the focus areas are located in the prefrontal lobe and the results are often consistent with studies such as fMRI and CT, and it can make up for some of the technology's shortcomings.

Imaging of life-long brain development is not only limited to the examination of developmental disorders in children and young adults but also in depicting the neurophysiological functions of the elderly. For the importance of age-related cortical haemodynamic effects in cognitive tasks, elderly subjects, compared to the young adults, had reduced HbO concentrations during VFT without left cerebral activation [62]. In a large sample of 325 healthy older adults, cortical oxidative activity decreased in the inferior frontal lobe junction but increased in the middle frontal lobe, indicating compensatory processes or cortical recombination [63]. Oxygenation in patients with Alzheimer disease (AD) often shows hemispherical lateral damage and reduced HbO concentrations (reflecting weakened cortical activation), especially in DLPFC and parietal cortex, through a VFT [60,64]. In spatial tasks, healthy subjects showed significant apical activation, while patients showed activation only in control tasks [64]. Studies have examined subcortical vascular dementia (SVD) patients. They found that cortical haemodynamics and metabolic response were reduced in patients with SVD in the motor cortex, and cerebral blood flow and oxygen metabolic rate were reduced, too [65]. In addition, another study used fNIRS to assess the effect of galantamine on fluency in AD patients between 4 and 8 weeks of treatment [66]. In short, these findings demonstrate the potential of fNIRS in assessing cortical oxygenation in developmental disorders and have advantages in studying children's low-health, elderly subjects or cortical actual function-related factors.

Conclusion

fNIRS is a highly practical and versatile imaging technology that has been widely used in many disciplines for its non-invasive, real-time, simple, bedside applications, and high practicality, especially in nerves. In the field of psychiatry, it has special significance for the monitoring and localization of blood oxygen metabolism in cerebral cortical tissue. It has been involved in many diseases and basic research. However, some shortcomings of fNIRS have been exposed in practice. For example, due to the imperfect instrument design or algorithm, the monitoring indicators in the clinical application are easy to be interfered, and the accuracy and stability are not enough. In this aspect, there is still a need for several basic types of research, such as controlling all kinds of possible interfering factors, improving hardware structure and optimizing the algorithm. In addition, the tolerance of patients in clinical practice, the control of time and the operability of the process, etc., need more accurate and

comprehensive consideration in the preliminary research, so that it can be more efficient and repeatable in practical application. So far, most fNIRS studies in psychiatric disorders are about prefrontal activation, among which VFT is the most popular paradigm. At first, for the use of a few channels, to avoid the influence of the hair, the prefrontal region is a good starting point for fNIRS research, but given the recent technological development (e.g. multi-channel system), areas of interest should be expanded, especially since neuropsychiatric disorders are mostly based on alterations in distributed cerebral networks. In addition, although VFT has been shown to be reliable as a simple example, because of the differences between patients and controls, it covers only a limited aspect of neurocognitive functions, which may partly explain why the relevant cortical activation seems to change relative to the specific diagnosis. Anyhow, fNIRS is a very good analysis testing technology and is rapidly developed in the field of spectral analysis. In conclusion, with the development of detection and analysis techniques, the fNIRS will be widely applied in psychiatric and brain science research in order to provide more reliable evidence for precision diagnosis and therapeutic strategies.

Authors' contributions

Fan Chang and Haozhe Li reviewed the literature and drafted the manuscript; Chen Chen and Chao Liu reviewed the literature and collected data; Shengyu Zhang reviewed the literature and analysed the data; Haozhe Li and Weixiong Cai conceived of the study protocol and participated in design and coordination of the study.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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