Journal of Psychiatric Research 109 (2019) 33–40

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Reduced prefrontal-temporal cortical activation during verbal fluency task in obsessive-compulsive disorder: A multi-channel near-infrared spectroscopy study

Jinmin Liao[a], Tian Li[a], Wentian Dong[b], Jiuju Wang[b], Ju Tian[b], Jin Liu[b], Wenxiang Quan[b,*,1], Jun Yan[a,**,1]

[a] Inpatient Unit, Peking University Sixth Hospital, Peking University Institute of Mental Health, Key Laboratory of Mental Health, NHC (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing 100191, China
[b] Department of Translational Medicine, Peking University Sixth Hospital, Peking University Institute of Mental Health, Key Laboratory of Mental Health, NHC (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Beijing 100191, China

ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Near-infrared spectroscopy
Verbal fluency task
Prefrontal cortex
Temporal cortex

ABSTRACT

Functional neuroimaging studies by near-infrared spectroscopy (NIRS) have focused on the role of the prefrontal cortex (PFC) in the pathophysiology of obsessive-compulsive disorder (OCD). However, the reported areas in the PFC were inconsistent in OCD, and correlations between hemodynamic response and clinical symptoms have not been investigated. This study aimed to evaluate the hemodynamic response related to the verbal fluency task (VFT) and assess the relationship between activation and clinical status in OCD patients using a 52-channel NIRS with a wide coverage over the prefrontal and temporal cortices. Seventy patients with OCD and 70 age-, gender- and education level-matched healthy control subjects were examined by NIRS. The relative concentration changes of oxygenated hemoglobin ([oxy-Hb]) were measured. The Yale-Brown obsessive-compulsive scale (Y-BOCS) was used to evaluate the severity of OCD symptoms. Compared to healthy controls group, OCD patients showed smaller [oxy-Hb] changes in most areas of the prefrontal and temporal cortex, including the bilateral orbitofrontal cortex (OFC), right dorsolateral prefrontal cortex (DLPFC), bilateral inferior prefrontal cortex (IPFC), bilateral frontopolar cortex (FPC), left superior temporal gyrus (STG), and bilateral middle temporal gyrus (MTG). Furthermore, the [oxy-Hb] changes in the right FPC were negatively correlated with the Y-BOCS obsessions score and Y-BOCS total score, and the [oxy-Hb] changes in the left OFC were negatively correlated with the Y-BOCS compulsions score. These results suggest that patients with OCD have reduced prefrontal-temporal cortex hemodynamic responses, and that the abnormalities of brain activation were associated with the severity of OCD symptoms.

1. Introduction

Obsessive-compulsive disorder (OCD) is one of the most common psychiatric disorders and is characterized by persistent unwanted thoughts (obsessions) and repetitive ritualistic behaviors (compulsions). The symptoms occupy much of the patient's time and energy and lead to impairment of social function. OCD is debilitating and difficult to treat, with a lifetime prevalence rate of 2%–3% in the general population (Weissman et al., 1994; Ruscio et al., 2010). Despite the high incidence and large burden of the OCD, the neurophysiological mechanisms are not yet clear.

Near-infrared spectroscopy (NIRS) is a noninvasive optical imaging method, which can obtain quantitative concentration changes of oxygenated hemoglobin ([oxy-Hb]), deoxygenated hemoglobin ([deoxy-Hb]), and total hemoglobin ([total-Hb]) associated with brain functional activity (Villringer and Chance, 1997). Compared with MRI and PET, NIRS gets a high time resolution, making it conceivable to show the activation of the brain in real time (Ferrari and Quaresima, 2012). Compared with EEG, NIRS is better at localizing the neural signals. In addition, with its relatively low maintenance costs, portability, high ecological validity, and lower sensitivity to motion artifacts, NIRS is particularly suitable for the assessment of the brain function in

* Corresponding author. Department of Translational Medicine, Peking University Sixth Hospital, 51 Hua Yuan Bei Road, Hai Dian District, Beijing, 100191, China.
** Corresponding author. Inpatient Unit, Peking University Sixth Hospital, 51 Hua Yuan Bei Road, Hai Dian District, Beijing, 100191, China.
E-mail addresses: quanwx302@aliyun.com (W. Quan), yanjun_peking@hotmail.com (J. Yan).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jpsychires.2018.11.006
Received 1 June 2018; Received in revised form 3 November 2018; Accepted 3 November 2018

psychiatric patients (Koizumi et al., 1999). NIRS has been applied in patients with depression, schizophrenia, bipolar disorder, dementia, and attention deficit hyperactivity disorder (Suto et al., 2004; Arai et al., 2006; Quan et al., 2015; Gu et al., 2017; Zhu et al., 2018). However, studies focused on the patients with OCD by NIRS are relatively few.

Functional neuroimaging studies by NIRS showed dysfunction in the prefrontal cortex (PFC) during executive tasks in OCD. Okada et al. (2013) used 24-channel NIRS to examine neurobiological function in 12 adult patients with OCD during the Stroop color-word task and revealed that [oxy-Hb] change of the left lateral prefrontal cortex in OCD patients was markedly smaller than that in healthy control subjects. They also found that pediatric OCD patients (n = 12) had smaller [oxy-Hb] change in the frontopolar cortex (FPC) (Ota et al., 2013). The reduced [oxy-Hb] changes in the right dorsolateral prefrontal cortex (DLPFC) were reported during a verbal fluency task (VFT) in 20 OCD patients by using 42-channel NIRS (Hirosawa et al., 2013). Despite all the above studies in OCD by NIRS reporting a reduced hemodynamic response in the PFC, the areas in the PFC were different. The differences between these results may be explained by the different coverages of the PFC, the study populations, the difference of cognitive tasks and the relatively small sample sizes. Prefrontal cortical surface areas were segregated in orbital, dorsolateral, ventrolateral, and frontopolar regions (Yoon et al., 2007; Eickhoff et al., 2016). However, it remains unknown whether all the sub-regions of the PFC are associated with the pathophysiology of OCD. It is therefore urgent to investigate the brain activation changes in a large enough coverage of significant sub-regions of the PFC in a large sample of OCD patients by NIRS. In addition, correlations between concentration changes of [oxy-Hb] and symptom severity of OCD have not been investigated.

The VFT is a classical method for assessing cognitive activation during NIRS. Dan et al. (2013) investigated the neural correlates of VFT in healthy Japanese patients using NIRS and found the VFT activated the bilateral frontal-temporal regions. Meta-analysis reported that patients with OCD were significantly impaired in the performance of VFT, which is related to executive control processes (Shin et al., 2014). Previous studies have focused on the role of the PFC in the pathophysiology of OCD, and the studies on OCD as measured by NIRS did not evaluate other brain regions, such as the temporal cortex. Based on previous research applying other neuroimaging techniques in OCD (Fouche et al., 2017; Koh et al., 2018), we hypothesized that OCD patients also have reduced hemodynamic response in the temporal cortex as measured by NIRS.

Therefore, in the present study, we used a 52-channel NIRS system to investigate the characteristics of brain activation in a wide coverage of the prefrontal cortex and temporal cortex during performance of VFT in a larger group of patients with OCD and explored the relationships between activation in the prefrontal-temporal cortex and clinical symptoms. We hypothesized that the patients with OCD have smaller brain activation changes in the prefrontal and temporal cortices and that these alterations would be associated with clinical symptoms.

2. Materials and methods

2.1. Participants

The research was approved by the Research Ethics Committee of Peking University Sixth Hospital (Beijing, China). All subjects signed an informed consent after supplying comprehensive information about the research.

Eighty-six OCD patients were recruited from the outpatient units of Peking University Six Hospital. Enrollment criteria for the OCD patients included (a) a diagnosis of OCD based on the *Diagnostic and Statistical Manual of Mental Disorders* Fourth edition (DSM-IV) criteria (First et al., 1997), confirmation of the diagnosis of OCD for each patient by two experienced psychiatrists; (b) an age between 16 and 55; (c) right-handedness; (d) years of education ≥6 years; and (e) a score on the Yale-Brown obsessive-compulsive scale (Y-BOCS) ≥8. Patients who presented with other psychiatric disorders, neurological disorders, a head injury, a serious medical condition, or a history of electroconvulsive therapy within six months were excluded. Y-BOCS was used to evaluate the severity of current symptoms in patients with OCD. The Y-BOCS has 10 items, with items 1 to 5 being used to evaluate for obsessions and items 6 to 10 being used to evaluate for compulsions. The total score of Y-BOCS is 40 points, including 0–7 for subclinical, 8–15 for mild, 16–23 for moderate, 24–31 for severe, and 32–40 for extreme (Goodman et al., 1989). In the study, all patients of OCD suffered from at least mild symptoms. Yale-Brown obsessive-compulsive scale symptom checklist (YBOCS-SC; Goodman et al., 1989) was used to assess symptom dimensions. After data quality control, 16 patients of OCD were excluded because of handedness, comorbidity, motion artifact, or incomplete collection.

Seventy healthy control subjects were recruited through the local community. Enrollment criteria for healthy control subjects included (a) an age between 16 and 55; (b) right-handedness; and (c) years of education ≥6 years. All healthy controls had no history of major neurological or psychiatric disorders. The final sample comprised 70 patients and 70 healthy controls.

2.2. Task description

In the research, we used the Chinese version of VFT. A more detailed description of the experimental task was available elsewhere (Quan et al., 2015). In brief, the procedure consists of 3 periods, including a 30-s baseline, a 60-s task, and a 50-s rest after task. During the 60-s task period, three Chinese characters as '白'(which indicates white), '天'(which indicates sky), and '大'(which indicates big) were provided in order, and each character lasted 20 s. Participants were instructed verbally to make as many phrases as possible, beginning with each provided character during the task period. The total number of correct phrases of the three groups was recorded as the evaluation of cognitive function during VFT.

2.3. NIRS measurements

A 52-channel NIRS optical topography system (ETG-4000, Hitachi Medical Co., Tokyo, Japan) was used for data acquisition. The system generated two wavelengths (695 and 830 nm) of near-infrared light and measured the relative concentration of changes in [oxy-Hb], [deoxy-Hb], and [total-Hb] based on the modified Beer-Lambert law (Maki et al., 1995). The instrument consisted of 17 light emitters and 16 light detectors, which were arranged in a 3 × 11 array with an interprobe distance of 3.0 cm (see Fig. 1). The lowest probes were positioned along the Fp1-Fp2 line according to the international 10–20 systems of electroencephalogram electrode placement. The measurement area covered the bilateral dorsolateral PFC [Brodmann's area (BA) 9, 46], ventrolateral PFC (BA 44, 45, 47), orbitofrontal cortex (BA11), frontopolar cortex (BA10), superior temporal gyrus (BA22), middle temporal gyrus (BA21), and temporopolar area (BA38). The time resolution of absorption of NIRS was set at 0.1s.

2.4. NIRS data processing

The NIRS data analysis was performed using MATLAB 2013b (Mathworks, Sherborn, MA) and NIRS-SPM (http://bisp.kaist.ac.kr/NIRS-SPM). The raw data were converted by calculating the concentration changes of [oxy-Hb], [deoxy-Hb], and [total-Hb] from optical density changes, according to the modified Beer-Lambert law (Maki et al., 1995). Then, the data were corrected for global drift by detrending using the discrete cosine transform algorithm. The precoloring method was used for temporal correlation estimation, and HRF was chosen for the low pass filter (Ye et al., 2009). The general linear

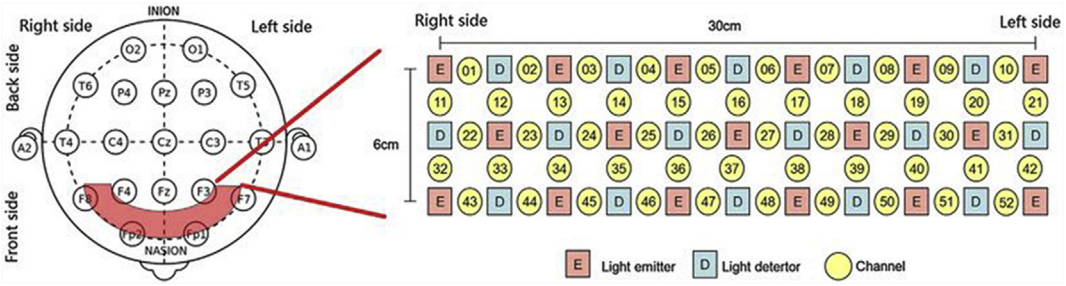

Fig. 1. Channel layout of 52-channel NIRS cap. Left: the position of the probe array (red band) based on the international 10–20 system. Right: 2-D topographic map. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

model was used for the NIRS data. The concentration changes of [oxy-Hb], [deoxy-Hb], and [total-Hb] were calculated for each channel in each individual subject. The β-values were estimated using a least-square fitting procedure maximizing model-to-data fitting (Bullmore et al., 1996), which represented the response amplitudes of brain during the task.

Grand averages of waveforms were performed separately in each channel for each group, which make it possible to monitor cerebral blood volumes in real time. The last 10s of the pre-task period was chosen for the time-range of the pre-task baseline (Takizawa et al., 2008). Baseline corrections and filtered data were used before data export. Discrete cosine transform algorithm was used for the filtered. Then we calculated the grand average of waveforms in each group for every channel, respectively, for type of [oxy-Hb], according to the individual subjects' waveforms.

2.5. Statistical analyses

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22 (IBM Corporation, New York, USA), G*Power version 3.1.9.2 (Franz, Universitat Kiel, Germany) and MATLAB 2013b. Changes in [oxy-Hb] have been shown to be the most sensitive indicator of regional cerebral blood flow (Strangman et al., 2002), so our study focused on concentration changes of [oxy-Hb]. First, to find the areas of brain activation during VFT in each group, one-sample *t*-tests against zero were used in the OCD group and healthy controls group, respectively (Dan et al., 2013), and the results were shown in Fig. 2a and Fig. 2b. Second, independent sample *t*-tests were used to find the differences in brain activation between patients and the healthy controls group during the task period, and effect sizes were calculated, and the results were shown in Table 2 and Fig. 2c. The statistical results were corrected for multiple comparisons with a false discovery rate (FDR) method at $p < 0.05$(Singh and Dan, 2006). Third, the grand average waveforms of [oxy-Hb] concentration changes during VFT were calculated in both groups in Fig. 3.

For the OCD group, the correlations between the concentration changes of [oxy-Hb] (β-values) and Y-BOCS scores and the performance of VFT were assessed using Pearson's correlation coefficients in each channel. Statistical significance was.

considered at $p < 0.05$.

3. Results

3.1. Demographic data and clinical characteristics

Demographic and clinical data were shown in Table 1. There were no significant differences in age, gender, and education level between the two groups. The mean Y-BOCS score of OCD patients was (22.2 ± 6.6), which suggested that the patients presented moderate or severe OCD symptoms. Doubt/checking was the most frequent symptom dimension in the study. Thirty-four patients with OCD were unmedicated, and 36 patients with OCD received antidepressants, as follows: 15 patients received sertraline, 12 patients received fluvoxamine, 5 patients received paroxetine, 2 patients received escitalopram, 2 patients received fluoxetine, 2 patients received clomipramine, and 2 patients received venlafaxine. Four of them had two drugs combined. In addition, the score of VFT did not differ significantly between the two groups.

3.2. NIRS data analysis

3.2.1. Brain activation in each group

To assess the effect of brain activation on [oxy-Hb] during VFT, we used one-sample *t*-tests for each channel in the two groups, respectively. In the healthy controls group, a significant increase of [oxy-Hb] concentration changes during VFT were observed at 52 channels (Ch.1–52) (Fig. 2a). In the OCD group, there were 16 channels with significant increases of [oxy-Hb](Ch.16–17, 24–29, 33–36, 38–39, 45–46) (Fig. 2b). The FDR was adopted for multiple 52-channel testing correction. Obviously, OCD patients exhibited smaller brain activated areas than the healthy controls group.

3.2.2. Group comparison

Compared to the healthy controls group, the OCD group has much lower cortical activation in most channels. A significantly lower increase of [oxy-Hb] was found at 16 channels in the OCD group (Ch. 13–14, 18, 27–29, 35, 38–40, 42, 44–46, 50–51). Fig. 2c illustrates the results of group comparison, and black cycles were used to mark the channels which reached statistical significance. The 16 channels represented the brain area as follows: bilateral orbitofrontal cortex (OFC) (BA11, Ch. 27, 28, 35, 38, 39, 46, 50), right dorsolateral prefrontal cortex (DLPFC)(BA 46, Ch. 13), bilateral inferior prefrontal cortex (IPFC)(BA47, Ch. 28, 40, 45), bilateral frontopolar cortex (FPC) (BA10, Ch. 14, 18), bilateral middle temporal gyrus (MTG)(BA 21, Ch. 44, 51), and left superior temporal gyrus (STG)(BA22, Ch. 42) (Wang et al., 2017). Probabilistic locations of the significant channels in group-level analysis were demonstrated. More details were shown in Table 2.

3.2.3. Time course of [oxy-Hb] change

The grand average waveforms of [oxy-Hb] concentration changes during the VFT at all 52 channels between two groups were presented in Fig. 3. The grand average waveforms of [oxy-Hb] concentration changes in the healthy controls group increased during the task period, while those of the OCD group did not markedly change. In addition, we found the grand average waveforms of OCD group seems serrated and the healthy control group smooth in most channels.

3.3. Correlational analysis

In OCD group, we preformed the correlation analysis between the concentration change of [oxy-Hb] and the scores of Y-BOCS obsessions, Y-BOCS compulsions, Y-BOCS total, and VFT. There were negative correlations for the Y-BOCS obsessions scores with the concentration changes of [oxy-Hb] at channel 15($r = -0.372$, $p = 0.003$), for Y-

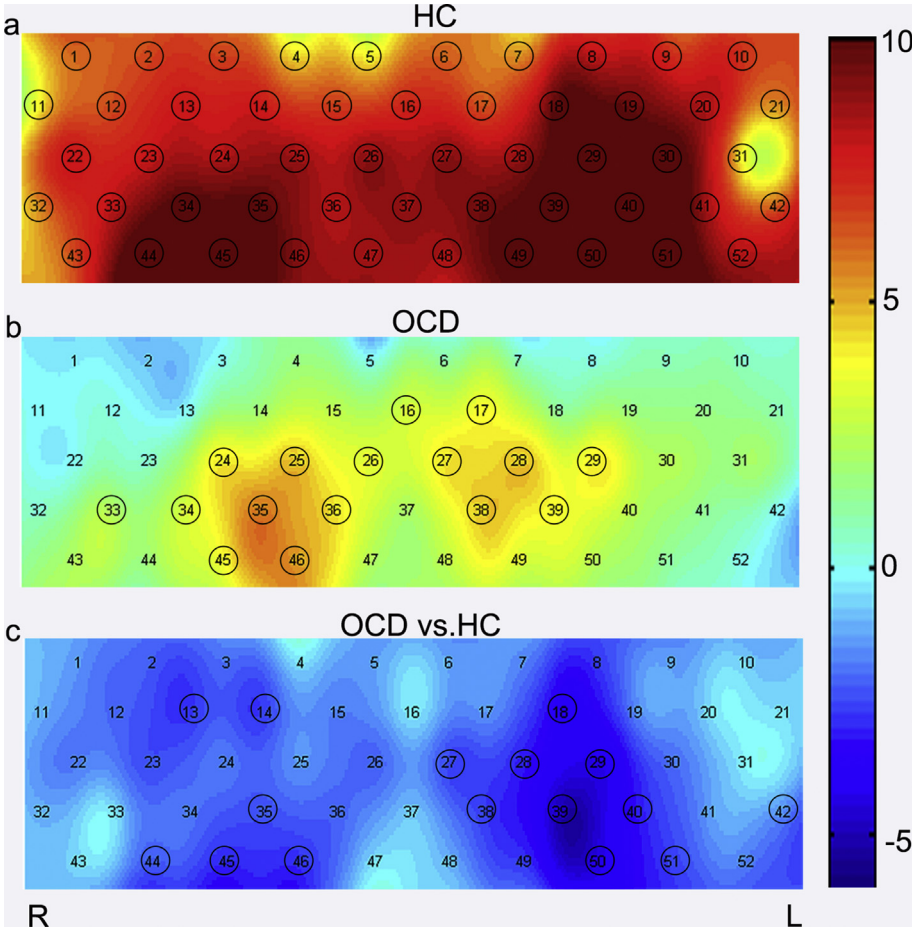

Fig. 2. Brain activation as measured by concentration changes of [oxy-Hb] in the healthy controls group and OCD group during VFT. a: Brain activation during VFT in healthy controls group; b: Brain activation during VFT in OCD group; c: The group comparison for brain activation between the OCD patients and healthy controls. Color bar represent *t* values. Black cycles were used to represent the channels reaching the statistical significance. $p < 0.05$, FDR correction. HC, healthy controls; OCD, obsessive-compulsive disorder; R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

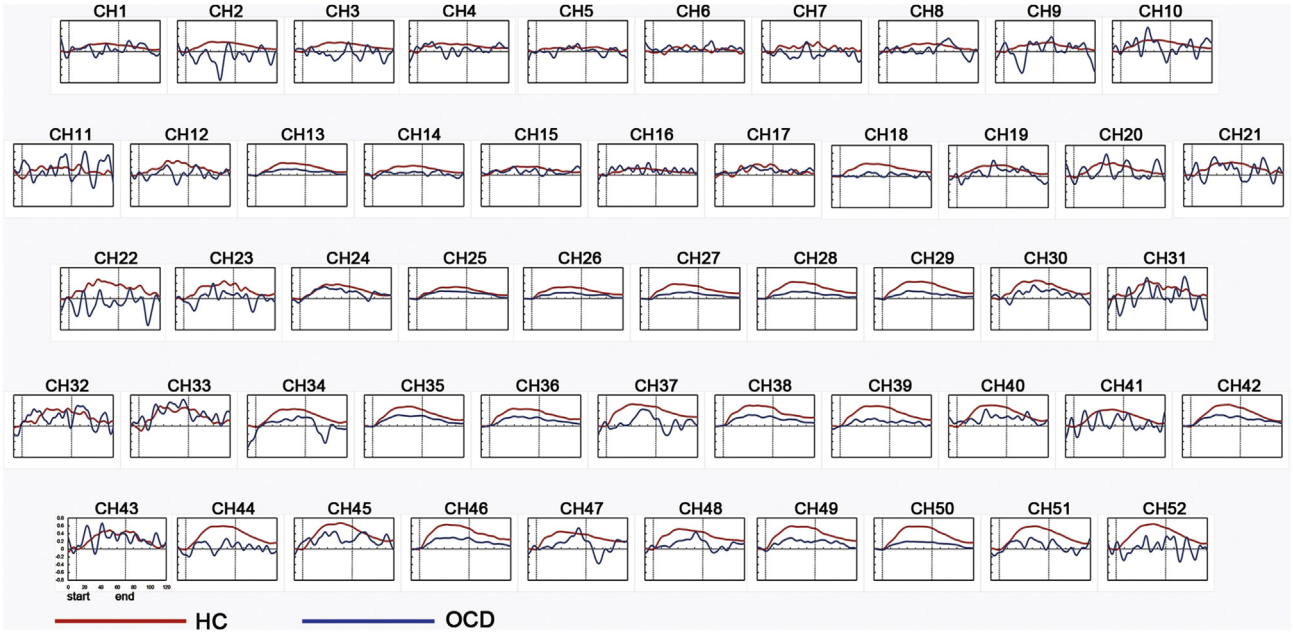

Fig. 3. Grand average waveforms showing changes in [oxy-Hb] concentration during VFT in the healthy controls group (red line) and the OCD group (blue line) for each of the 52 channels. The *x* axis shows the time course(s) and the *y* axis shows the change in [oxy-Hb] concentration (mM.cm). The first 10s was set as the pre-task baseline, the 10s–70s was set as task period, and the last 50s was set as the post-task period. The vertical lines indicate the start and end of VFT. HC, healthy controls; OCD, obsessive-compulsive disorder. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Demographic and clinical characteristics of patients with OCD and healthy controls.

Demographic and clinical variables	Patients with OCD (n = 70)	Healthy controls (n = 70)	Statistic[a]	*p* Value
Age, year: mean (S.D.)	27.6 (9.7)	29.9 (7.9)	1.535	0.127
Gender, male/female, no.	44/26	47/23	0.283	0.595
Education level, year: mean (S.D.)	14.3 (2.3)	14.8 (2.8)	1.153	0.251
VFT performance: mean (S.D.)	10.5 (3.9)	11.8 (4.0)	1.657	0.100
Duration of illness, month: mean (S.D.)	59.6 (69.2)			
Y-BOCS: mean (S.D.)				
Obsessions	11.6 (3.9)			
Compulsions	10.7 (3.8)			
Total score	22.2 (6.6)			
Obsessive-compulsive symptoms: n (%)				
Contamination/cleaning	52 (74.3)			
Doubt/checking	60 (85.7)			
Symmetry/ordering	36 (51.4)			
Unacceptable/taboo thoughts	57 (81.4)			
Hoarding	22 (31.4)			

OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown obsessive-compulsive scale.
[a] Independent samples *t*-test for continuous variables, χ^2 test for categorical variables.

BOCS compulsions scores with channel 37($r = -0.340$, $p = 0.006$) and channel 48($r = -0.346$, $p = 0.005$), for the Y-BOCS total scores with channel 15($r = -0.332$, $p = 0.008$). The channel 15 represented the brain area of the right FPC (BA 10, MNI coordinates [32 68 0]), and channel 37 and channel 48 both represented the left OFC (BA11, MNI coordinates [9 68–20] and [1 62–24]). There was positive correlation between the VFT scores and the concentration changes of [oxy-Hb] at channel 42($r = 0.326$, $p = 0.019$). The channel 42 represented the brain area of the superior temporal gyrus (BA22, MNI coordinates [-69 -34 17]).

4. Discussion

In the present study, we found that the [oxy-Hb] changes during VFT were significantly smaller at the prefrontal and temporal cortices in the OCD group than in the healthy controls group, and the [oxy-Hb] changes in the right FPC were negatively correlated with the severity of obsessions and the severity of OCD symptoms; the [oxy-Hb] changes in the left OFC were negatively correlated with the severity of compulsions. These results support the hypothesis that the dysfunctions of the prefrontal and temporal cortices are present in OCD, and the dysfunctions are associated with the symptoms of OCD.

In comparison to the healthy controls group, the patients group did not show a significant difference in performance of VFT. VFT related to executive function and languages. Meta-analysis showed that patients with OCD were significantly impaired in executive function (Shin et al., 2014). In our study, we did not find similar results, maybe because we chose only one relatively simple task for executive function. Previous studies showed that there were no significant differences between the healthy controls and the patients with schizophrenia or depressive disorder in the performance of VFT, but they also found the [oxy-Hb] increase patterns varied among groups by NIRS during VFT (Suto et al., 2004). It may suggest NIRS is a more sensitive method for finding the impairment of the brain, and it may be used for early detection of cognition deficiency in OCD patients.

In our study, there were 52 channels significantly activated during VFT in the healthy controls group, while there were only 16 channels in the OCD group. It was obvious that the activated area in the OCD patients was smaller than in the healthy controls. Healthy controls activated at all channels during VFT, which showed the regions of the bilateral prefrontal cortex and temporal cortex activated. The overall activation patterns for VFT in healthy controls by NIRS were consistent with the previous studies (Dan et al., 2013; Quan et al., 2015). Changes in the concentrations of [oxy-Hb] are deemed to represent alterations in regional cerebral blood volume, reflecting brain activation. The OCD group had smaller activated areas during VFT, which may mean there was a shortage of reserve energy in the prefrontal and temporal regions (Hoshi and Tamura, 1993; Ohmae et al., 2006).

Table 2
The channels of significantly different brain activation during VFT between OCD group and healthy controls group.

Channel	Brain area	BA	MNI coordinates			*T*	*p* Value	Cohen's d
			X	Y	Z			
13	Dorsolateral prefrontal cortex (R)	46	60	24	23	−3.022	0.003	0.510
14	Frontopolar area (R)	10	49	52	10	−2.691	0.008	0.460
18	Frontopolar area (L)	10	−41	60	1	−3.968	< 0.001	0.672
27	Orbitofrontal cortex (L)	11	−1	68	−15	−2.830	0.005	0.478
28	Orbitofrontal cortex (L)	11	−26	66	−13	−3.472	< 0.001	0.586
29	Inferior prefrontal gyrus (L)	47	−49	49	−9	−4.339	< 0.001	0.735
35	Orbitofrontal cortex (R)	11	48	52	−13	−2.045	0.008	0.455
38	Orbitofrontal cortex (L)	11	−11	66	−20	−2.954	0.004	0.500
39	Orbitofrontal cortex (L)	11	−37	58	−14	−5.583	< 0.001	0.943
40	Inferior prefrontal gyrus (L)	47	−52	40	−11	−3.167	0.002	0.537
42	Superior temporal gyrus (L)	22	−69	−34	17	−2.453	0.015	0.043
44	Middle temporal gyrus (R)	21	64	5	−17	−2.695	0.008	0.456
45	Inferior prefrontal gyrus (R)	47	49	46	−17	−3.633	< 0.001	0.613
46	Orbitofrontal cortex (R)	11	38	58	−17	−3.472	< 0.001	0.588
50	Orbitofrontal cortex (L)	11	−45	45	−18	−4.162	< 0.001	0.703
51	Middle temporal cortex (L)	21	−58	11	−26	−2.793	0.006	0.472

R, right; L, left; BA: Brodmann's area; MNI: Montreal neurological institute.

In group comparison, we found the OCD group had reduced brain activation in the prefrontal cortex and temporal cortex, including bilateral OFC, IPFC, FPC, right DLPFC, left STG, and bilateral MTG. The reduction in [oxy-Hb] activation during the VFT period implies that patients with OCD might have difficulty in acquiring adequate blood supply to compensate for the consumed oxygen. This compensation mechanism is crucial for proper neuronal activity. Previous studies reported hypofunction of the PFC in OCD patients by NIRS, including right DLPFC (Hirosawa et al., 2013), left lateral PFC (Okada et al., 2013), and FPC (Ota et al., 2013). In the study, we found more dysfunctional regions in OCD patients by using the 52-channel NIRS with a wide coverage over the prefrontal and temporal cortices, such as OFC, IPFC, STG, and MTG. It may be helpful for us to further understand the pathogenesis of OCD by NIRS. Furthermore, we find the grand average waveforms of OCD group were serrated in most channels, while the patterns of waveforms in the healthy control groups were smooth. We think the serrated waveforms may be a characteristic of OCD patients that potentially distinguish them from healthy controls. However, further studies are needed.

We observed a lower activation in OFC during the task in the OCD group and found the abnormalities of OFC were associated with the severity of compulsions. Our results were in accordance with previous reports by MRI. Some studies found increases in OFC gray matter volume (Togao et al., 2010; Rotge et al., 2010) and white matter volume in OCD (Togao et al., 2010). Patients with OCD also showed decreased function connectivity between the central orbitofrontal cortex and dorsomedial striatum (Jung et al., 2017). Some studies also reported that symptom severity of OCD was associated with the gray matter volume in OFC (Koprivová et al., 2009; Venkatasubramanian et al., 2012). Taken together, the structural and functional alterations of OFC are the most frequently reported neuroimaging findings in OCD patients (Jung et al., 2017). Dysfunction of the cortico-striato-thalamo-cortical (CSTC) routing through the OFC is thought to play the main role in the pathophysiology of OCD (Milad and Rauch, 2012; Fettes et al., 2017; Jung et al., 2017). OFC has been implicated in shifting between habitual action and goal-directed action by evaluating the consequences of action (Gremel and Costa, 2013; Samara et al., 2017). The imbalance between two actions may underlie distorted behaviors in OCD and other decision-making disorders. Studies have reported OCD patients had impaired action control during a goal-directed learning task (Gillan et al., 2011). We found the brain activation of OFC was associated with the severity of compulsions. Compulsions are repetitive, stereotyped behaviors, such as repeated checking of locks and excessive hand washing. Most patients clearly know the compulsions are valueless and unreasonable, but they feel driven to perform, relying on habits. It is possible that compulsions are due to the impairment of switching between habits and goal-directed behaviors, which is caused by the dysfunction of OFC.

Besides OFC, patients with OCD also had significantly reduced changes in [oxy-Hb] concentrations than controls in other sub-regions of the PFC, including DLPFC, IPFC, and FPC, and the [oxy-Hb] changes in FP were negatively correlated with the Y-BOCS obsessions scores and the Y-BOCS total scores. Some studies reported brain structural and functional abnormalities in the DLPFC and IPFC in OCD patients. OCD patients exhibited decreased function activation of the DLPFC, caudate, and putamen during planning (van den Heuvel et al., 2005), and goal-directed performance was related to reduced functional connectivity between the putamen and the DLPFC in OCD patients (Vaghi et al., 2017). De Wit et al.(2014) performed a multicenter voxel-based morphometry mega-analysis between 412 adult OCD patients and 368 healthy subjects and found the volume of the inferior frontal gyrus was significantly smaller, relative to healthy comparison subjects. Britton et al. (2010) found reduced activation of the left inferior frontal gyrus (BA 47) was present in pediatric OCD patients in the set-shifting contrast. Furthermore, in the present study, patients with OCD exhibited hypoactivation in FPC and the correlations between activation of FPC and OCD symptoms, which were consistent with previous studies. Ota et al. (2013) showed the [oxy-Hb] changes in FPC were significantly smaller in pediatric OCD patients than in healthy controls during Stroop color-word by using NIRS. Zhu et al. (2016) found OCD patients had increased amplitude of low-frequency fluctuations value in the left FPC. The Y-BOCS obsessions scores negatively correlated with the left frontal pole volume (Venkatasubramanian et al., 2012). Boschin et al. (2015) reported that the essential functions of FPC in cognition were markedly different from the other prefrontal regions. They showed that FPC was implicated in the ability to learn rapidly about novel objects and rules by using an animal model. Their results suggested that the FPC makes a significant contribution to the exploration and rapid acquisition of novel behavioral options, and FPC plays an important role in complex, higher-order behavior (Boschin et al., 2015). The impairment of FPC may induce the symptoms like repeated thoughts and behavior, which may participate in the occurrence of OCD. In addition, Previous studies showed that OFC and FPC have been consistently implicated across a wide range of psychiatric disorders, such as OCD (Jung et al., 2017), major depressive disorder (Cheng et al., 2016) and schizophrenia (Takizawa et al., 2008; Liao et al., 2015), which may influence the symptomatology or global functioning of psychiatric diseases (Boschin et al., 2015; Fettes et al., 2017). Further studies are needed to explore the relationship between the activation in OFC and FPC and the global functioning of OCD patients.

Furthermore, our study also showed that [oxy-Hb] changes in the OCD group during VFT were significantly smaller than in the healthy controls in STG and MTG. Compared with previous studies on OCD by NIRS (Hirosawa et al., 2013; Okada et al., 2013; Ota et al., 2013), our findings suggest that [oxy-Hb] changes are not limited to the frontal cortex, and the dysfunction of the temporal cortex might be also associated with the pathophysiology of OCD. Studies found that the volume reduced in STG (Choi et al., 2006; Tang et al., 2015). A significant decrease in white matter in the right STG extending into the insula was correlated with symptoms of OCD (Lázaro et al., 2014). Tan et al. (2013) reported increased volume of the bilateral middle temporal gyrus in OCD patients. Giménez et al. (2017) found that OCD patients showed increased fractional amplitude of low-frequency fluctuation values in the middle temporal lobe. Compared to PFC, the temporal cortex has been relatively less recognized in OCD functional neuroimaging studies. The temporal cortex is involved in memory, visuospatial processing, and visceral sensory, which were impaired in patients with OCD (Olson et al., 2007; Rotge et al., 2008; Brascamp et al., 2010). However, the specific contributions of the temporal cortex to OCD are yet unclear, and the detailed mechanism needs to be further studied.

Some limitations should be considered in our study. First, 36 patients with OCD were taking antidepressants at the time of the study. Antidepressants have been reported to affect hemodynamic responses in patients with major depressive disorder (Takamiya et al., 2017), but it is not clear whether antidepressants influence hemodynamic responses in OCD patients. Takeda et al. (2017) found there were no significant differences in [oxy-Hb] changes among medication statuses by NIRS in OCD patients. It should also be noted that, in our study group, comparison of medicated (n = 36) and nonmedicated OCD patients (n = 34) showed no significant differences as regards the concentration changes of [oxy-Hb] (These results reported in online supplementary Table S1 and Fig. S1). It might be that the medications have little effect on our OCD patients. Second, the spatial resolution of NIRS is lower than that of fMRI or PET; however, most of our findings were consistent with the previous studies on OCD identified by other neuroimaging modalities. The spatial resolution is within an acceptable range, and in consideration of the availability of NIRS, NIRS could be used widely in clinical practice.

5. Conclusions

To our knowledge, this is the first study in a relatively large sample

of OCD patients to present the characters of [oxy-Hb] changes and assess the relationships between activation and clinical status during VFT by using a 52-channel NIRS with a wide coverage over the prefrontal and temporal cortical surface area. In the study, we confirmed the areas of smaller brain activation in the PFC as previously reported in OCD patients by NIRS. Besides, we found more dysfunctional regions in OCD patients, such as OFC, IPFC, STG, and MTG. In addition, we found the relationships between the dysfunctions of FPC and OFC and OCD symptoms. Such findings may help us to further understand the pathogenesis of OCD by NIRS.

Role of the funding source

This work was supported in part by the National Natural Science Foundation of China (81601171).

Declaration of interest

None.

CRediT authorship contribution statement

Jinmin Liao: Data curation, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft. **Tian Li:** Data curation, Formal analysis, Investigation, Methodology, Validation. **Wentian Dong:** Investigation, Project administration, Resources, Software, Supervision. **Jiuju Wang:** Investigation, Project administration, Resources, Software, Supervision. **Ju Tian:** Investigation, Project administration, Resources, Software, Supervision. **Jin Liu:** Investigation, Project administration, Resources, Software, Supervision. **Wenxiang Quan:** Conceptualization, Methodology, Software, Validation, Visualization. **Jun Yan:** Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

Acknowledgements

The authors thank Zhichao Xia for the support of NIRS data analysis, from Beijing Normal University, Beijing, China.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.11.006.

References

Arai, H., Takano, M., Miyakawa, K., Ota, T., Takahashi, T., Asaka, H., Kawaguchi, T.A., 2006. Quantitative near-infrared spectroscopy study: a decrease in cerebral hemoglobin oxygenation in Alzheimer's disease and mild cognitive impairment. Brain Cognit. 61 (2), 189–194.

Boschin, E.A., Piekema, C., Buckley, M.J., 2015. Essential functions of primate frontopolar cortex in cognition. Proc. Natl. Acad. Sci. U.S.A. 112 (9), E1020–E1027.

Brascamp, J.W., Kanai, R., Walsh, V., van Ee, R., 2010. Human middle temporal cortex, perceptual bias, and perceptual memory for ambiguous three-dimensional motion. J. Neurosci. 30 (2), 760–766.

Britton, J.C., Rauch, S.L., Rosso, I.M., Killgore, W.D., Price, L.M., Ragan, J., Chosak, A., Hezel, D.M., Pine, D.S., Leibenluft, E., Pauls, D.L., Jenike, M.A., Stewart, S.E., 2010. Cognitive inflexibility and frontal-cortical activation in pediatric obsessive-compulsive disorder. J. Am. Acad. Child Adolesc. Psychiatry 49 (9), 944–953.

Bullmore, E., Brammer, M., Williams, S.C., Rabe-Hesketh, S., Janot, N., David, A., Mellers, J., Howard, R., Sham, P., 1996. Statistical methods of estimation and inference for functional MR image analysis. Magn. Reson. Med. 35 (2), 261–277.

Cheng, W., Rolls, E.T., Qiu, J., Liu, W., Tang, Y., Huang, C.C., Wang, X., Zhang, J., Lin, W., Zheng, L., Pu, J., Tsai, S.J., Yang, A.C., Lin, C.P., Wang, F., Xie, P., Feng, J., 2016. Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. Brain 139, 3296–3309.

Choi, J.S., Kim, H.S., Yoo, S.Y., Ha, T.H., Chang, J.H., Kim, Y.Y., Shin, Y.W., Kwon, J.S., 2006. Morphometric alterations of anterior superior temporal cortex in obsessive-compulsive disorder. Depress. Anxiety 23 (5), 290–296.

Dan, H., Dan, I., Sano, T., Kyutoku, Y., Oguro, K., Yokota, H., Tsuzuki, D., Watanabe, E., 2013. Language-specific cortical activation patterns for verbal fluency tasks in Japanese as assessed by multichannel functional near-infrared spectroscopy. Brain Lang. 126 (2), 208–216.

Eickhoff, S.B., Laird, A.R., Fox, P.T., Bzdok, D., Hensel, L., 2016. Functional segregation of the human dorsomedial prefrontal cortex. Cerebr. Cortex 26 (1), 304–321.

Ferrari, M., Quaresima, V., 2012. A brief review on the history of human functional infrared spectroscopy (fNIRS) development and fields of application. Neuroimage 63 (2), 921–935.

Fettes, P., Schulze, L., Downar, J., 2017. Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: promising therapeutic targets in psychiatric illness. Front. Syst. Neurosci. 11, 25.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders –Clinician Version (SCID-CV). American Psychiatric Press, Inc., Washington, DC, USA.

Fouche, J.P., du Plessis, S., Hattingh, C., Roos, A., Lochner, C., Soriano-Mas, C., Sato, J.R., Nakamae, T., Nishida, S., Kwon, J.S., Jung, W.H., Mataix-Cols, D., Hoexter, M.Q., Alonso, P., OCD Brain Imaging Consortium,de Wit, S.J., Veltman, D.J., Stein, D.J., van den Heuvel, O.A., 2017. Cortical thickness in obsessive-compulsive disorder: multisite mega-analysis of 780 brain scans from six centres. Br. J. Psychiatry 210 (1), 67–74.

Gillan, C.M., Papmeyer, M., Morein-Zamir, S., Sahakian, B.J., Fineberg, N.A., Robbins, T.W., de Wit, S., 2011. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. Am. J. Psychiatry 168 (7), 718–726.

Giménez, M., Guinea-Izquierdo, A., Villalta-Gil, V., Martínez-Zalacaín, I., Segalàs, C., Subirà, M., Real, E., Pujol, J., Harrison, B.J., Haro, J.M., Sato, J.R., Hoexter, M.Q., Cardoner, N., Alonso, P., Menchón, J.M., Soriano-Mas, C., 2017. Brain alterations in low-frequency fluctuations across multiple bands in obsessive-compulsive disorder. Brain Imaging Behav. 11 (6), 1690–1706.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. Arch. Gen. Psychiatr. 46 (11), 1006–1011.

Gremel, C.M., Costa, R.M., 2013. Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. Nat. Commun. 4, 2264.

Gu, Y., Miao, S., Han, J., Zeng, K., Ouyang, G., Yang, J., Li, X., 2017. Complexity analysis of fNIRS signals in ADHD children during working memory task. Sci. Rep. 7 (1), 829.

Hirosawa, R., Narumoto, J., Sakai, Y., Nishida, S., Ishida, T., Nakamae, T., Takei, Y., Fukui, K., 2013. Reduced dorsolateral prefrontal cortical hemodynamic response in adult obsessive-compulsive disorder as measured by near-infrared spectroscopy during the verbal fluency task. Neuropsychiatric Dis. Treat. 9, 955–962.

Hoshi, Y., Tamura, M., 1993. Dynamic multichannel near-infrared optical imaging of human brain activity. J. Appl. Physiol. 75 (1985), 1842–1846.

Jung, W.H., Yücel, M., Yun, J.Y., Yoon, Y.B., Cho, K.I., Parkes, L., Kim, S.N., Kwon, J.S., 2017. Altered functional network architecture in orbitofronto-striato-thalamic circuit of unmedicated patients with obsessive-compulsive disorder. Hum. Brain Mapp. 38 (1), 109–119.

Koh, M.J., Seol, J., Kang, J.I., Kim, B.S., Namkoong, K., Chang, J.W., Kim, S.J., 2018. Altered resting-state functional connectivity in patients with obsessive-compulsive disorder: a magnetoencephalography study. Int. J. Psychophysiol. 123, 80–87.

Koizumi, H., Yamashita, Y., Maki, A., Yamamoto, T., Ito, Y., Itagaki, H., Kennan, R., 1999. Higher-order brain function analysis by trans-cranial dynamic near-infrared spectroscopy imaging. J. Biomed. Optic. 4 (4), 403–413.

Koprivová, J., Horácek, J., Tintera, J., Prasko, J., Raszka, M., Ibrahim, I., Höschl, C., 2009. Medial frontal and dorsal cortical morphometric abnormalities are related to obsessive-compulsive disorder. Neurosci. Lett. 464 (1), 62–66.

Lázaro, L., Ortiz, A.G., Calvo, A., Ortiz, A.E., Moreno, E., Morer, A., Calvo, R., Bargallo, N., 2014. White matter structural alterations in pediatric obsessive-compulsive disorder: relation to symptom dimensions. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 54, 249–258.

Liao, J., Yan, H., Liu, Q., Yan, J., Zhang, L., Jiang, S., Zhang, X., Dong, Z., Yang, W., Cai, L., Guo, H., Wang, Y., Li, Z., Tian, L., Zhang, D., Wang, F., 2015. Reduced paralimbic system gray matter volume in schizophrenia: correlations with clinical variables, symptomatology and cognitive function. J. Psychiatr. Res. 65, 80–86.

Maki, A., Yamashita, Y., Ito, Y., Watanabe, E., Mayanagi, Y., Koizumi, H., 1995. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med. Phys. 22 (12), 1997–2005.

Milad, M.R., Rauch, S.L., 2012. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cognit. Sci. 16 (1), 43–51.

Ohmae, E., Ouchi, Y., Oda, M., Suzuki, T., Nobesawa, S., Kanno, T., Yoshikawa, E., Futatsubashi, M., Ueda, Y., Okada, H., Yamashita, Y., 2006. Cerebral hemodynamics evaluation by near-infrared time-resolved spectroscopy: correlation with simultaneous positron emission tomography measurements. Neuroimage 29, 697–705.

Okada, K., Ota, T., Iida, J., Kishimoto, N., Kishimoto, T., 2013. Lower prefrontal activity in adults with obsessive-compulsive disorder as measured by near-infrared spectroscopy. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 43, 7–13.

Olson, I.R., Plotzker, A., Ezzyat, Y., 2007. The Enigmatic temporal pole: a review of findings on social and emotional processing. Brain 130 (Pt 7), 1718–1731.

Ota, T., Iida, J., Sawada, M., Suehiro, Y., Yamamuro, K., Matsuura, H., Tanaka, S., Kishimoto, N., Negoro, H., Kishimoto, T., 2013. Reduced prefrontal hemodynamic response in pediatric obsessive-compulsive disorder as measured by near-infrared spectroscopy. Child Psychiatr. Hum. Dev. 44 (2), 265–277.

Quan, W., Wu, T., Li, Z., Wang, Y., Dong, W., Lv, B., 2015. Reduced prefrontal activation during a verbal fluency task in Chinese-speaking patients with schizophrenia as measured by near-infrared spectroscopy. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 58, 51–58.

Rotge, J.Y., Guehl, D., Dilharreguy, B., Cuny, E., Tignol, J., Bioulac, B., Allard, M., Burbaud, P., Aouizerate, B., 2008. Provocation of obsessive-compulsive symptoms: a

quantitative voxel-based meta-analysis of functional neuroimaging studies. J. Psychiatry Neurosci. 33 (5), 405–412.
Rotge, J.Y., Langbour, N., Guehl, D., Bioulac, B., Jaafari, N., Allard, M., Aouizerate, B., Burbaud, P., 2010. Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. Neuropsychopharmacology 35 (3), 686–691.
Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol. Psychiatry 15, 53–63.
Samara, Z., Evers, E.A.T., Goulas, A., Uylings, H.B.M., Rajkowska, G., Ramaekers, J.G., Stiers, P., 2017. Human orbital and anterior medial prefrontal cortex: intrinsic connectivity parcellation and functional organization. Brain Struct. Funct. 222 (7), 2941–2960.
Shin, N.Y., Lee, T.Y., Kim, E., Kwon, J.S., 2014. Cognitive functioning in obsessive-compulsive disorder: a meta-analysis. Psychol. Med. 44 (6), 1121–1130.
Singh, A.K., Dan, I., 2006. Exploring the false discovery rate in multichannel NIRS. Neuroimage 33, 542–549.
Strangman, G., Culver, J.P., Thompson, J.H., Boas, D.A., 2002. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage 17 (2), 719–731.
Suto, T., Fukuda, M., Ito, M., Uehara, T., Mikuni, M., 2004. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biol. Psychiatry 55 (5), 501–511.
Takamiya, A., Hirano, J., Ebuchi, Y., Ogino, S., Shimegi, K., Emura, H., Yonemori, K., Shimazawa, A., Miura, G., Hyodo, A., Hyodo, S., Nagai, T., Funaki, M., Sugihara, M., Kita, M., Yamagata, B., Mimura, M., 2017. High-dose antidepressants affect near-infrared spectroscopy signals: a retrospective study. Neuroimage Clin 14, 648–655.
Takeda, T., Sumitani, S., Hamatani, S., Yokose, Y., Shikata, M., Ohmori, T., 2017. Prefrontal cortex activation during neuropsychological tasks might predict response to pharmacotherapy in patients with obsessive-compulsive disorder. Neuropsychiatric Dis. Treat. 13, 577–583.
Takizawa, R., Kasai, K., Kawakubo, Y., Marumo, K., Kawasaki, S., Yamasue, H., Fukuda, M., 2008. Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study. Schizophr. Res. 99 (1–3), 250–262.
Tan, L., Fan, Q., You, C., Wang, J., Dong, Z., Wang, X., Chen, K., Xiao, Z., Jiang, K., 2013. Structural changes in the gray matter of unmedicated patients with obsessive-compulsive disorder: a voxel-based morphometric study. Neurosci. Bull. 29 (5), 642–648.
Tang, W., Huang, X., Li, B., Jiang, X., Li, F., Xu, J., Yang, Y., Gong, Q., 2015. Structural brain abnormalities correlate with clinical features in patients with drug-naïve OCD: a DARTEL-enhanced voxel-based morphometry study. Behav. Brain Res. 294, 72–80.
Togao, O., Yoshiura, T., Nakao, T., Nabeyama, M., Sanematsu, H., Nakagawa, A., Noguchi, T., Hiwatashi, A., Yamashita, K., Nagao, E., Kanba, S., Honda, H., 2010. Regional gray and white matter volume abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. Psychiatr. Res. 184 (1), 29–37.
Vaghi, M.M., Vértes, P.E., Kitzbichler, M.G., Apergis-Schoute, A.M., van der Flier, F.E., Fineberg, N.A., Sule, A., Zaman, R., Voon, V., Kundu, P., Bullmore, E.T., Robbins, T.W., 2017. Specific frontostriatal circuits for impaired cognitive flexibility and goal-directed planning in obsessive-compulsive disorder: evidence from resting-state functional connectivity. Biol. Psychiatry 81 (8), 708–717.
van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Cath, D.C., van Balkom, A.J., van Hartskamp, J., Barkhof, F., van Dyck, R., 2005. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. Arch. Gen. Psychiatr. 62 (3), 301–309.
Venkatasubramanian, G., Zutshi, A., Jindal, S., Srikanth, S.G., Kovoor, J.M., Kumar, J.K., Janardhan Reddy, Y.C., 2012. Comprehensive evaluation of cortical structure abnormalities in drug-naïve, adult patients with obsessive-compulsive disorder: a surface-based morphometry study. J. Psychiatr. Res. 46 (9), 1161–1168.
Villringer, A., Chance, B., 1997. Non-invasive optical spectroscopy and imaging of human brain function. Trends Neurosci. 20 (10), 435–442.
Wang, J., Lv, B., Quan, W., Wydell, T.N., Tian, J., Wang, P., Liu, J., Dong, W., 2017. Right fronto-temporal activation differs between Chinese first-episode and recurrent Major Depression Disorders during a verbal fluency task: a near-infrared spectroscopy study. Psychiatry Res. Neuroimaging. 264, 68–75.
Weissman, M.M., Bland, R.C., Canino, G.J., Greenwald, S., Hwu, H.G., Lee, C.K., Newman, S.C., Oakley-Browne, M.A., Rubio-Stipec, M., Wickramaratne, P.J., et al., 1994. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J. Clin. Psychiatr. 55 (Suppl. l), 5–10.
Ye, J.C., Tak, S., Jang, K.E., Jung, J., Jang, J., 2009. NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. Neuroimage 44 (2), 428–447.
Yoon, J.H., Hoffman, J.N., D'Esposito, M., 2007. Segregation of function in the lateral prefrontal cortex during visual object working memory. Brain Res. 1184, 217–225.
Zhu, Y., Fan, Q., Zhang, H., Qiu, J., Tan, L., Xiao, Z., Tong, S., Chen, J., Li, Y., 2016. Altered intrinsic insular activity predicts symptom severity in unmedicated obsessive-compulsive disorder patients: a resting state functional magnetic resonance imaging study. BMC Psychiatr. 16, 104.
Zhu, Y., Quan, W., Wang, H., Ma, Y., Yan, J., Zhang, H., Dong, W., Yu, X., 2018. Prefrontal activation during a working memory task differs between patients with unipolar and bipolar depression: a preliminary exploratory study. J. Affect. Disord. 225, 64–70.