Neuroscience Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

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

Reduced functional connectivity in the prefrontal cortex of elderly catatonia patients: A longitudinal study using functional near-infrared spectroscopy

Toshinori Nakamura[a], Daimei Sasayama[a], Tetsuya Hagiwara[a], Hisashi Kito[b], Shinsuke Washizuka[a]

[a] Department of Psychiatry, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
[b] North Alps Medical Center Azumi Hospital, 3207-1 Oaza Ikeda, Kitaazumigun Ikeda, Nagano 399-8695, Japan

ARTICLE INFO

Article history:
Received 31 July 2020
Received in revised form
24 September 2020
Accepted 22 October 2020
Available online xxx

Keywords:
Catatonia
fNIRS
Resting state functional connectivity
Prefrontal cortex
Major depressive disorder
Bipolar disorder

ABSTRACT

Catatonia is a syndrome that manifests in patients with mental disorders and general medical conditions. However, functional changes to the brain that cause catatonia remain unknown. In the present study, we used functional near-infrared spectroscopy (fNIRS) to assess spontaneous hemodynamic activities in the brain at the times of onset and resolution of catatonic symptoms in patients with catatonia. We used 22-channel and 49-channel fNIRS to examine hemodynamic activities in the prefrontal cortex (PFC), and both frontal and parietal cortices, respectively. A total of ten patients who were diagnosed with catatonia were included in the study. Resting state measurements were taken for five minutes at the time of the onset and resolution of catatonic symptoms. Analyses were performed for the prefrontal region and the motor cortex within the parietal-frontal region of the brain. Functional connectivity between the cerebral hemispheres was evaluated systematically based on spontaneous oscillation of Δ[HbO2]. In the PFC, the resting state functional connectivity (RSFC) was significantly lower in the catatonic state than in the eyes-closed non-catatonic state ($p = 0.047$). The study demonstrated that the RSFC in the PFC, measured using fNIRS, may be an objective indicator of the change in catatonic symptoms.

1. Introduction

Catatonia was first described by Kahlbaum in 1874 as a syndrome associated with irregularly repeating neurological symptoms including mutism, rigidity, staring, stereotypy, and stupor (Kahlbaum, 1874). Subsequently, catatonia has long been considered a subtype of schizophrenia as suggested by Kraepelin; however, as the concept of catatonia changed over time, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) suggests that catatonia can manifest in individuals with numerous disorders, including neurodevelopmental disorders, psychotic disorders, bipolar disorders, depressive syndromes, and other medical disorders (Tandon et al., 2013). In the elderly population, excitement, verbigeration, negativism, immobility/stupor, and staring are considered common manifestations of catatonia (Cuevas-Esteban et al., 2017). It is also important to note that catatonia can be life-threatening (Fink and Taylor, 2009). Catatonia is observed in approximately 10 %–25 % of patients who are admitted to a hospital under mental disorders (Walther and Strik, 2016).

There is evidence suggesting that benzodiazepines are effective in treatment of catatonia, but their efficacy is unknown for patients who developed catatonia as a result of chronic schizophrenia. In such cases, electroconvulsive therapy (ECT) is commonly selected for treatment (Walther and Strik, 2016).

Patients with catatonia often have difficulty undergoing examinations that are time-consuming. As a result, progress in the field of neuroimaging research for catatonia has been relatively slow. In previous studies, functional magnetic resonance imaging (fMRI) and single-photon emission computed tomography (SPECT) were used to measure local changes in the regional cerebral blood flow (rCBF) and regional cerebral metabolic rate. These studies identified functional disorder in the basal ganglia (Luchins et al., 1989; Northoff et al., 1999), reduced blood flow in the frontal lobe, posterior portion of the temporal lobe, and parietal lobe (Northoff et al., 2000; Satoh et al., 1993a, b), and metabolic disorder in the orbitofrontal area (Richter et al., 2010). Evidence from neuroimaging studies is even more limited in the elderly population. One study used SPECT to examine blood flow in elderly patients who developed catatonia as a result of late-onset schizophrenia, and demonstrated that there was hypo-perfusion in the striatum and thalamus, in addition to hyper-perfusion in the left lateral frontal cortex (Tsujino et al., 2011).

https://doi.org/10.1016/j.neures.2020.10.004
0168-0102/

A previous study using MRI found that there was reduced local gyrification index in the temporal gyrus and over the surface of the parietal and medial orbitofrontal gyrus (Hirjak et al., 2019), in addition to hyper-perfusion in the supplementary motor area at resting state (Walther et al., 2017).

Near-infrared spectroscopy (NIRS) is a technique developed over the past 35 years to measure the function of the brain and has been used in research for the past 20 years (Boas et al., 2014). In the field of psychiatry, an increasing number of research studies have reported the use of functional NIRS (fNIRS) (Ehlis et al., 2014). Additionally, radioisotopes are often used in SPECT and positron emission tomography (PET). NIRS monitors the brain activation by measuring the changes in rCBF. In particular, NIRS detects the incremental increases in oxygenated hemoglobin concentration ([oxy-Hb]) as well as the decrease in the deoxygenated hemoglobin concentration ([deoxy-Hb]). Such rCBF changes are considered to be reflective of the cortical activity. (Hock et al., 1997). fNIRS is advantageous in the sense that it enables non-invasive measurement of the brain activity over time (Scholkmann et al., 2014). One case study used fNIRS and reported that cognitive tasks led to transient hyperactivity of the left anterior PFC in a male patient with catatonia, whose symptoms included specific immobility, mutism, and stereotypy (Grignon et al., 2008). However, no studies to date have examined the activities of the brain in multiple patients at the time of onset or after remission of catatonia in a longitudinal manner.

In the present study, we used fNIRS to examine changes in brain activity before and after treatment for catatonia in the elderly population. As it is difficult for catatonia patients to perform tasks, we evaluated the stability of resting state functional connectivity (RSFC). RSFC is a measurement of low-frequency spontaneous activity (<0.1 Hz) in the brain during resting and sleep states, and was initially shown using fMRI (Biswal et al., 1995; Raichle, 2010). Previous studies have demonstrated a strong correlation of the low frequency blood oxygenation level dependent (BOLD) signal between areas in the brain that are anatomically apart but functionally linked. Stability of functional connectivity can be observed simultaneously with spontaneous BOLD signals that are strongly correlated and connected between two areas of the brain (Sheffield and Barch, 2016). This method has been used with fNIRS by Niu et al. (Niu and He, 2014) and was also adopted in studies of mental disorders (Wu et al., 2018; Zhu et al., 2017). According to previous SPECT and fMRI studies, patients with catatonia present with functional impairment in the frontal lobe (Galynker et al., 1997; Northoff et al., 2000; Satoh et al., 1993b), motor area in the parietal-frontal region, and in the supplementary motor area (Northoff et al., 1999; Payoux et al., 2004; Scheuerecker et al., 2009; Walther, 2015; Walther et al., 2017). In the present study, we used fNIRS to assess differences in changes in the oxyHb concentration at times of onset and resolution of catatonia symptoms (catatonic and non-catatonic states, respectively) between the frontal region and motor cortex, including the motor area, premotor area, and supplementary motor area.

2. Materials and methods

2.1. Subjects

A total of ten patients over the age of 50 who were admitted to Shinshu University Hospital were included in the study (Table 1). These included two men and eight women, with a mean age of 64.5 (9.2) years. Patients were admitted for schizophrenia (n = 4), bipolar disorder (n = 1), and major depressive disorder (n = 5). The diagnosis of catatonia was made if the patient met the criteria for both DSM-5 and Bush Francis Catatonia Rating Scale Screening Instrument (BFCSI). The severity of catatonia was measured using the Bush Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996). At the start of the study, the BFCSI and BFCRS scores of the study patients were 7.4 (1.5) and 16.9 (1.7), respectively (Table 2). The mean number of days from the initial test in the catatonic state to the follow-up test in the non-catatonic state was investigated. Resolution of catatonic symptoms was based on the diagnostic criteria and defined as a BFCSI score of zero for all patients. All diagnoses were made by two experienced psychiatrists and patients were excluded from the study if they had severe organic diseases, such as brain tumors or widespread cerebral infarction, identified through an MRI or computed tomography. The type and dose of antipsychotics, antidepressants, and benzodiazepines/ non-benzodiazepines were also examined. In the catatonic state and non-catatonic state, doses of antipsychotics, antidepressants, and benzodiazepine/ non-benzodiazepine anxiolytics and sleeping pills were converted to chlorpromazine, imipramine, and diazepam equivalents, respectively (Gardner et al., 2010; Inada and Inagaki, 2015; Woods, 2003) (Table 3). In addition, ECT administration and its frequency were examined. The study was approved by the Research Ethics Board of Shinshu University School of Medicine. As informed consent could not be obtained from patients during the catatonic state, the study was explained and written informed consent was received from each patient's legal representative. As the symptoms of catatonia resolved, written consent was received from the study patients.

2.2. Neuroimaging

fNIRS was performed for a total of five minutes at rest in the catatonic and non-catatonic states. As patients were unable to respond to commands properly in the catatonic state, the measurements were taken after confirming that they were at rest regardless of whether they had their eyes open. As catatonia resolved, patients were told to stay at rest, and the measurements were taken with their eyes open and closed, in order to investigate the influence of eye opening. NIRS measurements during catatonic state for experiments 1 and 2 were performed on the same day in each patient. However, NIRS measurements during non-catatonic state for experiments 1 and 2 were performed on different days in 3 patients (patient numbers 1, 7, and 9) (Table 1). We measured the changes in [oxy-Hb] and [deoxy-Hb] using an NIRS system (FOIRE-3000; Shimazu Corporation, Kyoto, Japan). [oxy-Hb] and [deoxy-Hb] levels were calculated by the Lambert-Beer law based on the absorption of the three wavelengths of near-infrared light (780, 805, and 830 nm) measured by the NIRS system. The NIRS system detects changes in hemoglobin concentrations at approximately 2–3 cm from the surface of the skull. The distance from the detector probe to each pair of emission was 3.0 cm. The measurement area between each pair was defined as a 'channel' (CH). In the first experiment, 22 channels were positioned in a 6 × 12-cm area covering the prefrontal cortices with CH1-22. In the second experiment, 49 channels were positioned in a 15 × 12-cm area covering the frontal and parietal cortices with CH1-49. The lowest probes in the frontal cortex were positioned along the Fp1-Fp2 line according to the International 10–20 system. (Fig. 1) (Kito et al., 2014). Using NIRS-SPM, the region of interest for each cortical area was determined by confirming that the overlap across each channel was at least 78 % (Zhu et al., 2017).

2.3. Statistical analysis

In order to remove the long-term drift of the baseline and higher-frequency cardiac and/or respiratory activity, and to filter out the white Gaussian noise signal, only signals within the range of 0.009 and 0.08 Hz were retained using a combination of temporal high-pass and low-pass (bidirectional fifth-order band pass) filters. (Meszlenyi et al., 2017).

Table 1
Demographic and clinical data of the participants.

Patient no.	Sex	Age	Diagnosis	ECT (n)	Days between the two NIRS measurements for Experiment 1	Days between the two NIRS measurements for Experiment 2
1	F	65	Major depressive disorder	50	322	280
2	F	71	Schizophrenia	25	101	101
3	F	70	Schizophrenia	21	125	125
4	M	59	Schizophrenia	17	175	175
5	F	65	Major depressive disorder	20	79	79
6	F	80	Major depressive disorder	27	38	38
7	M	57	Schizophrenia	69	169	175
8	F	73	Major depressive disorder	50	168	168
9	F	51	Major depressive disorder	11	63	56
10	F	54	Bipolar disorder	10	42	42
Mean (SD)		64.5 (9.2)		30.0 (19.6)	128.2 (85.6)	123.9 (76.5)

Table 2
Catatonia symptoms at the day of fNIRS measurements.

Patient no.	BFCSI[1]	BFCRS[2]	Catatonia symptoms
1	8	18	Immobility/stupor, mutism, staring, grimacing, stereotypy, mannerisms, negativism, withdrawal, ambitendency
2	6	17	Immobility/stupor, mutism, staring, stereotypy, rigidity, negativism, gegenhalten, automatic abnormality
3	6	16	Immobility/stupor, mutism, staring, rigidity, negativism, withdrawal, automatic abnormality
4	5	16	Excitement, stereotypy, mannerisms, verbigeration, negativism, impulsivity, perseveration, automatic abnormality
5	8	19	Immobility/stupor, mutism, staring, posturing/catalepsy, rigidity, negativism, waxy flexibility, withdrawal, gegenhalten, automatic abnormality
6	9	16	Staring, posturing/catalepsy, grimacing, echopraxia/echolalia, stereotypy, verbigeration, rigidity, negativism, withdrawal, impulsivity, automatic obedience, perseveration
7	10	17	Immobility/stupor, staring, posturing/catalepsy, grimacing, echopraxia/echolalia, stereotypy, mannerisms, verbigeration, negativism, withdrawal, automatic obedience, automatic abnormality
8	7	15	Immobility/stupor, mutism, staring, posturing/catalepsy, grimacing, verbigeration, withdrawal, automatic abnormality
9	7	20	Immobility/stupor, mutism, staring, posturing/catalepsy, rigidity, negativism, withdrawal, gegenhalten, automatic abnormality
10	8	15	Immobility/stupor, mutism, staring, posturing/catalepsy, verbigeration, rigidity, negativism, withdrawal, grasp reflex
Mean (SD)	7.4 (1.5)	16.9 (1.7)	

[1] BFCSI: Bush Francis Catatonia Rating Scale Screening Instrument.
[2] BFCRS: Bush Francis Catatonia Rating Scale.

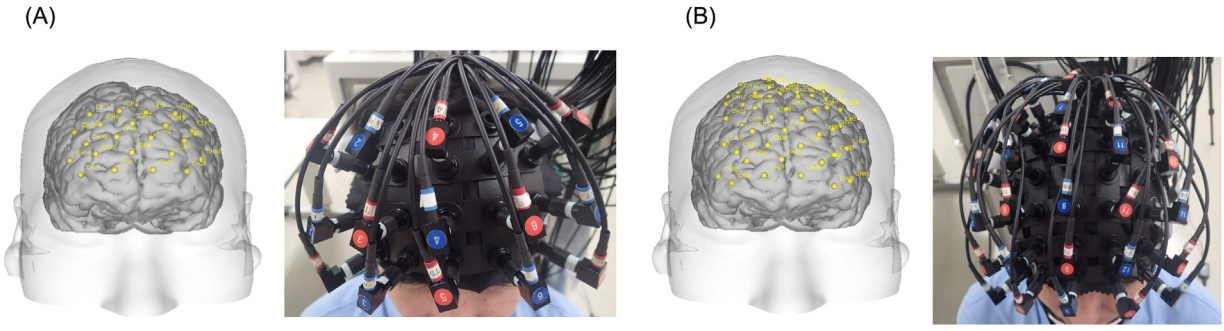

Fig. 1. (A) 22 channels were positioned the prefrontal cortex for Experiment1 and (B) 49 channels were positioned the frontal and parietal cortex of the frontal view for Experiment 2.

We defined the functional connectivity between the two channels as the Spearman's rank correlation coefficient between the changes in oxy-Hb levels in each channel. The mean functional connectivity was calculated between the symmetrical channel pairs in the target region of the brain (i.e. CH1-22 [whole brain] for experiment 1 and CH2, 3, 4, 6, 7, 8, 9, 10, 11, 12, and 14 [motor area, premotor area, and supplementary motor area] for experiment 2) for each participant in each state (i.e. catatonic state, eyes-closed non-catatonic state, and eyes-open non-catatonic state) (Fig. 2). The mean functional connectivity in each target region was compared between different states using the Wilcoxon signed-rank test. An average correlation coefficient for all channel pairs in each region was obtained by the following procedures. The Fisher Z transformation was applied to yield a z-value for each individual correlation

Table 3
Prescription data of the participants.

Patient no.	Experiment 1 and 2 (Catatonia)				Experiment 1 (Post-catatonia)				Experiment 2 (Post-catatonia)			
	Prescription	CPZs[1]	IMEs[2]	DEs[3]	Prescription	CPZs	IMEs	DEs	Prescription	CPZs	IMEs	DEs
1	mirtazapine	0	150	0	quetiapine, lorazepam	455	0	16.7	quetiapine, lorazepam	606	0	16.7
2		0	0	0	flunitrazepam, lorazepam	0	0	9.2	flunitrazepam, lorazepam	0	0	9.2
3	flunitrazepam, triazolam	0	0	15	tiapride	75	0	15	tiapride	75	0	15
4		0	0	0	clozapine	800	0	0	clozapine	800	0	0
5	diazepam	0	0	10	brotizolam, lorazepam	0	0	10	brotizolam, lorazepam	0	0	10
6	tiapride, lormetazepam, triazolam	75	0	5	tiapride	100	0	5	tiapride	100	0	5
7	diazepam	0	0	20	aripiprazole, flunitrazepam,lorazepam	600	0	30	aripiprazole, flunitrazepam,lorazepam	600	0	30
8	duloxetine, sertraline, alprazolam	0	313	7.5		0	0	0		0	0	0
9	lorazepam	0	0	25	zolpidem	0	0	2.5	zolpidem	0	0	2.5
10		0	0	0	estazolam	0	0	5	estazolam	0	0	5
Mean (SD)		7.5 (23.7)	46.3 (104.9)	8.3 (9.1)		203 (300.1)	0	9.3 (9.3)		218.1 (317.5)	0	9.3 (9.3)

[1] CPZ: Daily dose equivalence of antipsychotics (mg/day).
[2] IME: Daily dose equivalence of antidepressant (mg/day).
[3] DE: Daily dose equivalence of anxiolytics, sedatives and hypnotics (mg/day).

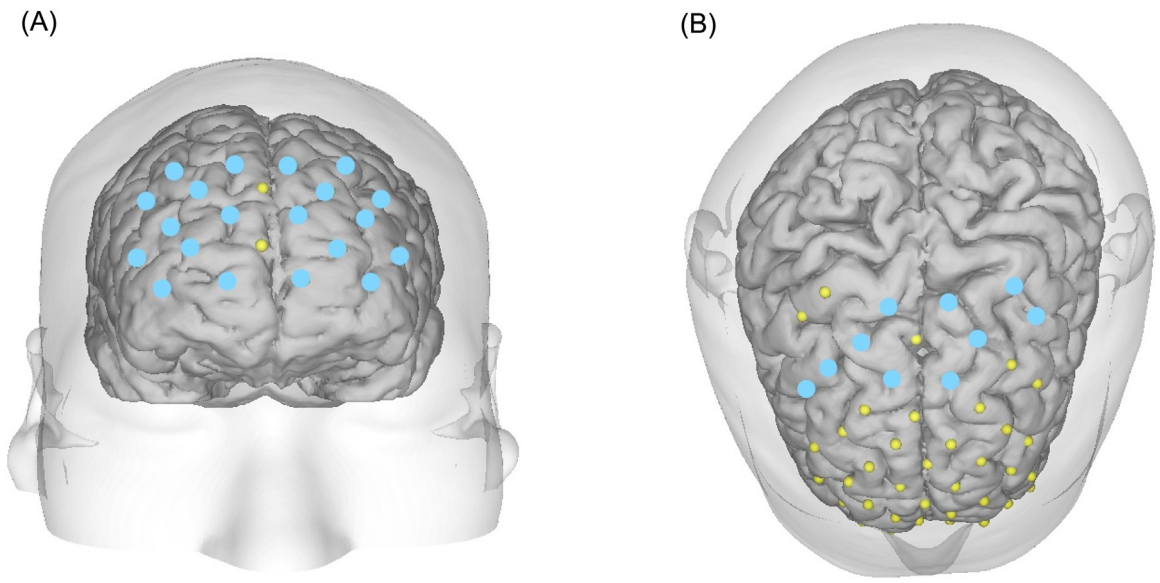

Fig. 2. (A) Blue dot were covered the channel pairs in the target region for Experiment 1 of the frontal view, (B) for Experiment2 of the superior view (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

coefficient. Then, we averaged the resulting z-values and applied inverse Fisher transformation to yield the average value of the correlation coefficients. *(*Wu et al., 2018*)*. SPSS25.0 (SPSS Inc., Chicago, IL, USA) software was used for all analyses.

3. Results

In the first experiment, which examined the prefrontal cortices, the mean functional connectivity during the catatonic state was significantly lower than during the eyes-closed non-catatonic state ($p = 0.047$). On the other hand, there was no significant difference in the mean functional connectivity between the catatonic state and eyes-open non-catatonic state. In the second experiment, which examined the frontal and parietal cortices, there were no significant differences in the mean functional connectivity during the catatonic state vs. eyes-closed non-catatonic state, catatonic state vs. eyes-open non-catatonic state, or eyes-closed state vs. eyes-open non-catatonic state (Table 4). No significant associations of functional connectivity were found with the number of ECT sessions or with the dose of benzodiazepines.

However, there was a significant reduction in the mean functional connectivity measured in the catatonic state compared with the eyes-closed and eyes-open non-catatonic states in patients with bipolar disorder and major depressive disorder (Experiment 1; $p = 0.028$ and 0.046, respectively). In patients with schizophrenia, there was no significant difference observed in functional connectivity measured in the catatonic state compared with those in the eyes-closed and eyes-open non-catatonic states. Furthermore, in the sub-group analysis of patients, with and without changes in the dose of benzodiazepine receptor agonist and use of antipsychotics, there was no significant difference observed in the mean functional connectivity between the catatonic and non-catatonic states.

On the individual level there was an increase in the mean functional connectivity in the symmetrical channel after the resolution of catatonia in most patients in the first experiment. However, the mean functional connectivity decreased after the resolution of catatonic symptoms in one patient with schizophrenia. The patient was not medically treated at the time of catatonia onset, and was subsequently treated using benzodiazepine receptor agonists, specifically 1 mg of lorazepam and 1 mg of flunitrazepam, when the symptoms of catatonia resolved.

4. Discussion

Catatonia is a syndrome that commonly manifests in patients with mental disorders; however, its pathogenesis remains to be fully elucidated. In the present study, we used fNIRS to examine changes in the activity of the brain in the catatonic and non-catatonic states in elderly patients. To our knowledge, this is the first study to use fNIRS to assess RSFC in patients with catatonia.

Our study examined the RSFC in the PFC (Experiment 1) and the motor cortex (Experiment 2) during catatonic and non-catatonic state. The study demonstrated that the functional connectivity defined as the correlation coefficient for the change in oxy-Hb levels was significantly higher in the non-catatonic state than in the catatonic state in the PFC. Thus, it can be concluded that the stability of RSFC was higher at the non-catatonic state. Many studies have examined the function of the PFC using fNIRS in patients with mental disorders. For example, one study demonstrated a correlation between the Global Assessment of Functioning score and reduced oxy-Hb concentration in the prefrontal region, especially the frontal pole of patients with schizophrenia whilst performing different tasks (Takizawa et al., 2008). Similarly, another study reported that task-related change in oxy-Hb in the frontal region was not as significant in patients with depression than it was in healthy individuals, and that patients with bipolar disorder and schizophrenia had a longer time course to reach the centroid value of the average waveform of oxy-Hb than those with depression (Takizawa et al., 2014). Using SPECT, patients with akinetic catatonia were found to have reduced perfusion to the frontal lobe and temporal lobe (Galynker et al., 1997; Northoff et al., 2000; Satoh et al., 1993b). At rest, functional connectivity of the PFC was found to be reduced in patients with mood disorders compared with healthy individuals (Zhu et al., 2017), and connectivity between areas, such as the frontal cortex, was shown to be reduced as a result of abnormal functional connectivity associated with cognitive impairment in schizophrenia patients (Sheffield and Barch, 2016). These findings are consistent to those of our study which demonstrate a positive correlation between the activity of the PFC and subsequent stability of RSFC in the non-catatonic state. This

Table 4
(A) Mean values of RSFC in the region of interest for each examination. (B) Correlation coefficients of RSFC between regions of interest for each examination.

(A)

		Average	SD
Experiment 1	Catatonia	0.432	0.237
	Post-catatonia (eyes-closed)	0.605	0.116
	Post-catatonia (eyes-open)	0.583	0.165
Experiment 2 (CH2−4,6−12,14)	Catatonia	0.484	0.223
	Post-catatonia (eyes-closed)	0.43	0.214
	Post-catatonia (eyes-open)	0.42	0.21

(B)

	Comparison	Z score	p value
Experiment 1	Catatonia and Post-catatonia (eyes-closed)	1.988	0.047
	Catatonia and Post-catatonia (eyes-open)	1.682	0.093
	Post-catatonia (eyes-closed) and Post-catatonia (eyes-open)	−0.255	0.799
Experiment 2 (CH2−4,6−12,14)	Catatonia and Post-catatonia (eyes-closed)	−0.968	0.333
	Catatonia and Post-catatonia (eyes-open)	−1.07	0.285
	Post-catatonia (eyes-closed) and Post-catatonia (eyes-open)	0.561	0.575

suggests that resolution of neurological symptoms may improve function of the frontal lobe, which subsequently increases the positive correlation between the activity of the PFC and stability of the RSFC.

In the present study, all patients underwent ECT, which may have affected the outcome of fNIRS. For example, in previous studies using SPECT, ECT increased the cerebral blood flow in the frontal and temporal lobes (Escobar et al., 2000; Galynker et al., 1997). Using MRI, the volume of the mid-temporal lobes and anterior cingulate cortex was reported to increase after ECT in patients with treatment-resistant depression, and this increase in the left mid-temporal lobe was associated with improvements in clinical functions (Cano et al., 2017). Another study using fNIRS demonstrated that ECT significantly increases the oxy-Hb concentration in the frontal cortices to reach a normal range while performing verbal fluency tasks, suggesting that task-induced activation is positively correlated with the degree of improvement in symptoms associated with depression (Hirano et al., 2017). Similarly, fNIRS revealed a significant increase in cerebral blood flow to the left hemisphere compared to the right hemisphere in patients with schizophrenia immediately after ECT, whereas there was no difference between the hemispheres in patients with depression (Fujita et al., 2011). Collectively, these studies suggest that ECT improves the function of the PFC and subsequently increases the activity of the PFC bilaterally. These activities are likely to have played a role in the degree of increase in positive correlation between brain activity and stabilized RSFC.

A number of previous studies have suggested that activities in the motor area and supplementary motor area may change as catatonic symptoms develop. For example, a study using fMRI demonstrated an increased level of perfusion in the supplementary motor area at rest (Walther et al., 2017). Similarly, task-associated neurological activities decreased in the motor area and supplementary motor area of the parietal region as catatonic symptoms developed. Specifically, Northoff et al. reported that the activity of the contralateral motor cortex was reduced in patients with catatonia during a task with the right hand (Northoff et al., 1999). Payoux et al. also showed that activation of supplementary motor area, left primary sensory motor area, bilateral lateral prefrontal cortex, and inferior parietal cortex were impaired in akinetic schizophrenia patients during a task with the right hand (Payoux et al., 2004). Furthermore, Scheuerecker et al. reported that patients who remitted from catatonia showed lower activity in the supplementary motor area and prefrontal parietal cortex during a right-handed motor task (Scheuerecker et al., 2009).

In the present study, we found no significant differences in the functional connectivity in the motor area, premotor area, and/or supplementary motor area, i.e., we were unable to detect changes in the activity of these areas at the onset or resolution of catatonic symptoms using fNIRS. In a previous study, Sebastian et al. measured neurological activities in schizophrenia patients at the time of onset of catatonic symptoms and in schizophrenia patients without catatonia in comparison with healthy individuals. Whereas, in another study, Northoff et al. and Payoux et al. measured neurological activities in patients with schizophrenia and other psychotic disorders at the time of onset of catatonic symptoms in comparison with healthy individuals. Similarly, Scheuerecker et al. measured neurological activities in schizophrenia patients at the time of resolution of catatonic symptoms in comparison to healthy individuals. On the other hand, we performed a longitudinal study comparing the same patient population at the times of onset and resolution of catatonic symptoms. Moreover, previous studies consisted of mainly patients with schizophrenia, while our study included patients with bipolar disorder and major depressive disorder as well as those with schizophrenia. Thus, these differences in the patient population may have led to differences in the study findings. Furthermore, our sample size was relatively small compared with that reported by Walther et al., which included 15 patients with schizophrenia and catatonia, 27 patients with schizophrenia without catatonia, and 41 controls. Thus, significant findings may have been observed in our study if we had a larger sample size.

At the onset of catatonic symptoms, it can often be difficult for patients to respond to commands. Indeed, we observed patients who either had their eyes closed at all times, open at all times, or both open and closed during the measurements. In the case of fMRI, the stability of RSFC is considered high in auditory and sensorimotor areas during the eyes-closed state, and in visual and attention areas during the eyes-open state (Agcaoglu et al., 2019; Wei et al., 2018). However, there is no evidence to suggest that these factors affect the connectivity of the PFC. Therefore, it is unlikely that having the eyes open or closed was responsible for observed changes in fNIRS signals in the PFC at the onset of catatonic symptoms.

In one of the patients with schizophrenia, the correlation in oxy-Hb concentration decreased in the PFC as catatonic symptoms resolved. We hypothesized that this may be due to ECT and the fact that measurements were taken when the patient had improved activities of daily living. Either way, the reason for this observation remains unclear. However, it is important to note that the correlation in oxy-Hb concentration for the symmetrical channel may decrease after the resolution of catatonic symptoms.

There are several limitations in this study. First, this was a longitudinal study and there was a large variation in terms of the time period between the two study time points. Second, there was variation in medications used in the catatonic and non-catatonic states. Previous studies suggested that both the usage (Kohmura et al., 2013) and dosage (Takamiya et al., 2017) of antidepressants affect fNIRS measurements obtained during verbal fluency tasks. Interestingly, one fMRI study also demonstrated that the use of antidepressants increased the functional connectivity of the frontal lobe even at resting state (Dichter et al., 2015). However, it should be noted that in this study RSFC was higher in the non-catatonic state than in the catatonic state despite the higher average dose of antidepressants prescribed during catatonia in this study. Therefore, the difference in RSFC between catatonic and non-catatonic states observed in the present study cannot be explained by the difference in antidepressant medications between the two states. Third, the change in the functional connectivity cannot only be attributed to improvements in catatonia, but also to ECT. Previous studies showed that schizophrenia patients with catatonia treated with ECT are liable to relapse, leading to increased number of ECT sessions (Suzuki et al., 2005, 2006). Indeed, some of the patients in our study required a great number of ECT sessions due to prolonged or relapsing catatonia symptoms. Fourth, the study patients were diagnosed by unstructured medical consultation. However, the diagnosis was confirmed by two or more experienced psychiatrists. Fifth, the sample size was small, and no healthy control group was included. Furthermore, we did not correct for multiple testing in our analyses. Therefore, future studies with larger sample size are necessary to confirm our findings. Moreover, comparison with healthy controls and analysis stratified by psychiatric diagnosis will lead to a further understanding of the pathophysiology of catatonia.

5. Conclusion

To the best of our knowledge, this is the first study to use fNIRS to examine the RSFC in patients with catatonia. Our study demonstrated an increase in the positive correlation of oxy-Hb in the PFC as catatonic symptoms resolved in patients, suggesting that there were improvements in the function of the frontal lobe. This observation may be a marker to assess the resolution of catatonic symptoms. As fNIRS is minimally invasive and can be performed relatively easily, it may be valuable to perform additional studies in a larger patient population to evaluate its use in catatonia patients.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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