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Fukushima Medical University

学　位　論　文

Frontal activity measured by near-infrared spectroscopy in patients taking different atypical antipsychotic drugs: A cross-sectional study

(光トポグラフィー検査による抗精神病薬内服患者の前頭葉機能の測定)

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神経精神医学分野

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1. Introduction

Impaired cognitive function plays a major role in psychiatric disorders such as schizophrenia (SC) (Censits et al., 1997; Heaton et al., 2001). A meta-analysis of 36 studies that examined abnormal cerebral metabolism in patients with SC found a decrease in frontal lobe function that became more pronounced as the duration of the disorder increased (Davidson and Heinrichs, 2003; Hill et al., 2004). On the other hand, mounting evidence shows that these atypical antipsychotics improve cognitive function (Keefe et al., 1999, 2004, 2006; Potkin et al., 2001).

Several studies have reported that atypical antipsychotics increase dopamine release in the prefrontal cortex (Kuroki et al., 1999; Gessa et al., 2000; Ichikawa et al., 2001; Heidbreder et al., 2001), which may lead to improved cognitive function in patients with SC (Kumari. 2015). Although the improvement in cognitive function brought by antipsychotics varies with each medication (Wang J 2013), the effects of atypical antipsychotics on cerebral function in the frontal lobe remain unknown.

Near-infrared spectroscopy (NIRS) is a noninvasive and useful method that measures only the function of the cerebral cortex, not deep tissue, and has a high temporal resolution (0.1 s). Recent reviews have found that activation during a variety of frontal lobe tasks is lower in patients with SC than in healthy controls (HCs) (Pu et al., 2016, Itakura et al., 2017).

Therefore, in the present study, to clarify the differential effects of antipsychotics

on frontal lobe function, we compared brain function in patients with SC who were receiving olanzapine (OLZ), a multi-acting receptor-targeted antipsychotic, or risperidone (RIS), a serotonin-dopamine antagonist, with HCs using NIRS.

2. Methods

2.1. Participants

The study participants were 20 non-randomized, non-consecutive inpatients and outpatients with SC treated with OLZ (n=10) or RIS (n=10), as well as 10 HCs who were matched for age (Table 1). SC was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. All diagnoses were made by two experienced psychiatrists, and the comorbidity of mental illness was ruled out for all participants. All participants were right-handed (score > 70), according to the Edinburgh Handedness Inventory (Oldfield, 1971). The clinical symptoms of SC were evaluated by trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) on the same day as the NIRS sequences. This study was approved by the ethics committee of Fukushima Medical University, and all patients provided their consent to participate after having been informed of the methods and purpose of the study.

2.2. NIRS measurement and cognitive tasks

We used a 52-channel NIRS machine (Hitachi ETG-4000; Hitachi Medical Corporation, Tokyo, Japan) (Maki et al., 1995) to measure relative changes in oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) using two wavelengths of near-infrared light (695 and 830 nm) in accordance with the modified Beer–Lambert law. The NIRS probes were fixed with 3 × 11 shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in Electroencephalogram (Okamoto et al., 2004). This arrangement can measure [oxy-Hb] levels from the bilateral prefrontal and superior temporal cortical surface regions (Tsuzuki et al., 2007).

NIRS signals were measured using the methods of Takizawa et al. (2008). The cognitive task used was a 60-s verbal fluency task (VFT; letter version). Concentration changes in oxy-Hb and deoxy-Hb ([oxy-Hb] and [deoxy-Hb]) were observed during the VFT.

2.3. Statistical analysis

Statistical analysis for between-group comparisons was performed using the unpaired *t*-test. The Mann-Whitney *U* test was used if normality was not maintained. Regarding the NIRS data, mean [oxy-Hb] levels during the task period were calculated, and then analysis of variance (ANOVA) was used to compare the three groups. We used one-way ANOVA for analysis, with a p level < 0.05 considered to indicate statistical

significance. When normality was not maintained, comparisons between the three groups were performed using the Kruskal-Wallis method. All statistical analyses were performed using IBM SPSS Statistics Version 21 (IBM Inc., Armonk, NY), MATLAB R2011 (Math Works Inc., Natick, MA), and Prism 6.0 software (GraphPad Software, Inc., San Diego, CA).

3. Results

The clinical characteristics of the study participants are shown in Table 1. The three groups were well matched in terms of gender (χ^2=1.875, df=2, p=0.392) and age (Kruskal-Wallis χ^2 (2, n=30) = 2.586, p=0.274). No significant differences were observed in antipsychotic dosages (two-sample t-test, t=1.959, p=0.072), the PANSS Total (two-sample t-test, t=0.378, p=0.710) , Positive (Mann-Whitney U test, U=49, p=0.939), Negative (two-sample t-test, t=–0.788, p=0.220)scores, or the task performance (one-way ANOVA, F(2,27) = 2.292, p=0.12). The changes in [oxy-Hb] in the frontal and temporal region in the three groups are shown in Figure 1A. In the OLZ group, the changes in [oxy-Hb] were comparable to those seen in the HC group. The changes in [oxy-Hb] were smaller in the RIS group than in the HC group. In the prefrontal region (CH46–49), a re-increase in [oxy-Hb] was seen in the RIS group after the task was completed; this is a typical and well-known pattern in patients with SC (Kinou et al., 2013; Suto et al., 2004; Takizawa et al., 2008, 2014). We then compared

the mean [oxy-Hb] levels between three groups in 52 channels.

Statistically significant differences were observed across the three groups in CH15 (Kruskal-Wallis χ^2 (2, n=26) = 8.089, p=0.018), CH18 (χ^2 (2, n=26) = 7.238, p=0.027), CH26 (χ^2 (2, n=26) = 8.411, p=0.015), CH29 (χ^2 (2, n=25) = 7.033, p=0.030), CH35 (χ^2 (2, n=27) = 6.461, p=0.040), CH36 (χ^2 (2, n=24) = 6.245, p=0.044), CH37 (χ^2 (2, n=22) = 10.927, p=0.004), CH39 (χ^2 (2, n=30) = 8.712, p=0.013), CH40 (χ^2 (2, n=22) = 11.161, p=0.004), CH46 (χ^2 (2, n=28) = 9.715, p=0.008), CH47 (χ^2 (2, n=23) = 13.321, p=0.001), CH48 (χ^2 (2, n=22) = 11.094, p=0.004), and CH50 (χ^2 (2, n=27) = 6.692, p=0.035), CH52 (χ^2 (2, n=24) = 7.110, p=0.029). Post-hoc testing using Dunn's test showed that the mean [oxy-Hb] levels of OLZ and HC were larger than RIS in CH46 (p<0.05) (Fig 1(B)).

In frontal regions (CH25–28, CH36–38, CH46–49), statistically significant differences were observed across the three groups (Kruskal-Wallis χ^2 (2, n=284) = 72.500, p<0.001), and the HC group had the largest change in [oxy-Hb].

4. Discussion

Notably, the changes in [oxy-Hb] levels in the OLZ group were larger than those in the RIS group in the prefrontal region; this suggests that OLZ improves hemodynamic patterns and brain function in the prefrontal region more effectively than RIS. OLZ ranks better than RIS for overall cognitive score (Désaméricq et al., 2013),

and a meta-analysis revealed that OLZ was superior to haloperidol in improving negative symptoms and depression, whereas no differences were found between RIS and haloperidol (Zhang et al., 2013). Both OLZ and RIS have been found to increase dopamine release in the medial prefrontal cortex (Kuroki et al., 1999; Gessa et al., 2000; Ichikawa et al., 2001; Heidbreder et al., 2001). On the other hand, OLZ blocks the *N*-methyl–d-aspartate receptor antagonist, ketamine, from inducing an increase in [^{14}C]2-deoxyglucose uptake, whereas RIS does not affect this uptake in the medial frontal cortex (Duncun et al., 2000). Taken together, OLZ may enhance frontal brain function, which can lead to improvements in negative symptoms, depression, and cognition in patients with SC.

In this study, different changes in [oxy-Hb] levels were observed in the RIS and OLZ groups, suggesting that NIRS patterns may be affected by antipsychotic drugs. Previous studies (Suto et al., 2004; Takizawa et al., 2014) suggest that NIRS is useful biomarker for the diagnosis of major psychiatric disorders. On the other hand, Kohmura et al. (2013) showed that compared with trazodone and a placebo, mirtazapine increased changes in [oxy-Hb] levels. Furthermore, we previously reported a case in which NIRS patterns changed after the administration of antipsychotics and lithium (Miura et al., 2014). Taken together, antipsychotic drugs may have different effects on the frontal hemodynamic patterns detected by NIRS, which may be a marker of SC status.

This study did have several limitations. First, NIRS measurements have

insufficient spatial resolution and are limited to the monitoring of only the cortical surface (Kameyama et al., 2006). Furthermore, Takahashi et al. (2011) indicated that most of the changes in [oxy-Hb] during a VFT measured on the forehead, approximately in the frontal pole, would involve skin blood flow. However, we calculated mean [oxy-Hb] levels in frontal region during a 60-s VFT that were averaged at several channels, which suggests the validity of our results. Second, the participants in the present study were outpatients with mild or moderate symptoms who had been treated with antipsychotics for a number of years. Since heterogeneity and previous treatment effects exist, further longitudinal studies in first-episode patients are needed to confirm and expand upon our results. Third, some participants with SC received co-medication, and its contents were zotepine, levomepromazine, sodium valproate and so on. This might have affected the NIRS results. Finally, the sample size was quite small. Given these limitations, it is difficult to reach a definitive conclusion regarding the influence of specific drugs. Therefore, our results regarding NIRS should be considered preliminary.

In summary, we found significant differences in NIRS measurements between the OLZ and RIS groups, and the changes in [oxy-Hb] levels were larger in the OLZ than in the RIS group in the prefrontal region. These results suggest that antipsychotic drugs may have different effects on the frontal hemodynamic patterns detected by NIRS, which may reflect cerebral function in the frontal region. Because of small sample size

and heterogeneity, further studies with a larger sample size and a longitudinal study design in patients with first-episode SC are needed to verify our findings.

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Figure legend

Fig. 1. (A) Grand average of waveforms of oxy-Hb changes during verbal fluency task in the olanzapine (OLZ) (n = 10) (red line), risperidone (RIS) (n = 10) (blue line), and healthy control (HC) groups (n = 10) (green line). (B) Comparison of mean oxy-Hb levels between the OLZ (n = 10), RIS (n = 10) and HC groups (n = 10) in CH46 during the 60-s verbal fluency task.

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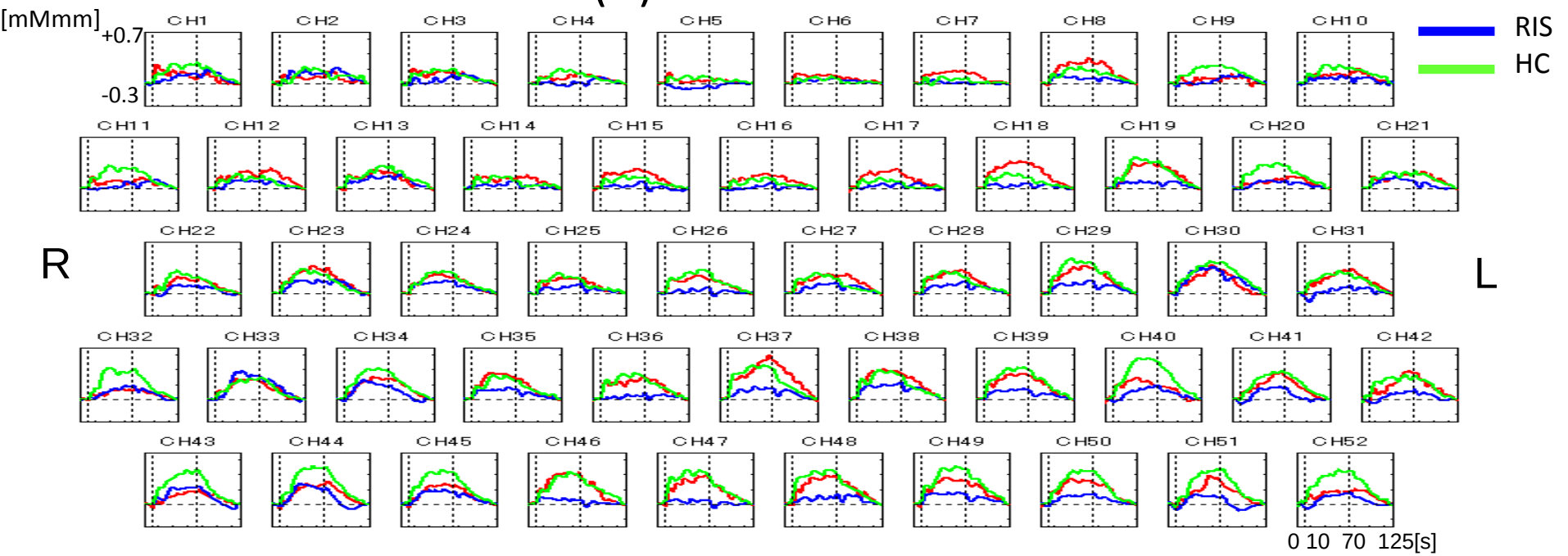
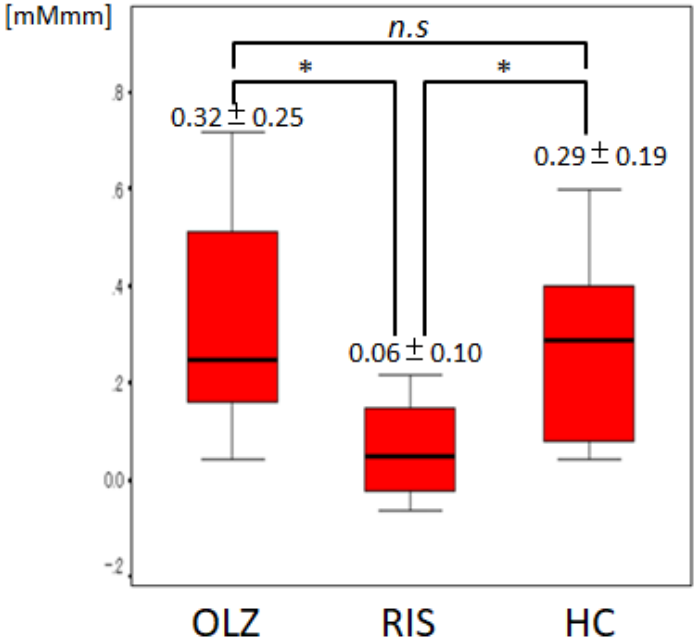
Author’s contributions

Shin-Ichi Niwa, and Hirooki Yabe designed the study and wrote the protocol. Itaru Miura and Soichi Kono managed the literature searches and analyses. Soichi Kono, Sachie Oshima, Rieko Suzuki carried out data acquisition. Masayuki Hikita and Akira Wada helped reviewing the content of the manuscript. Soichi Kono and Itaru Miura undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

(A) OLZ vs RIS vs HC



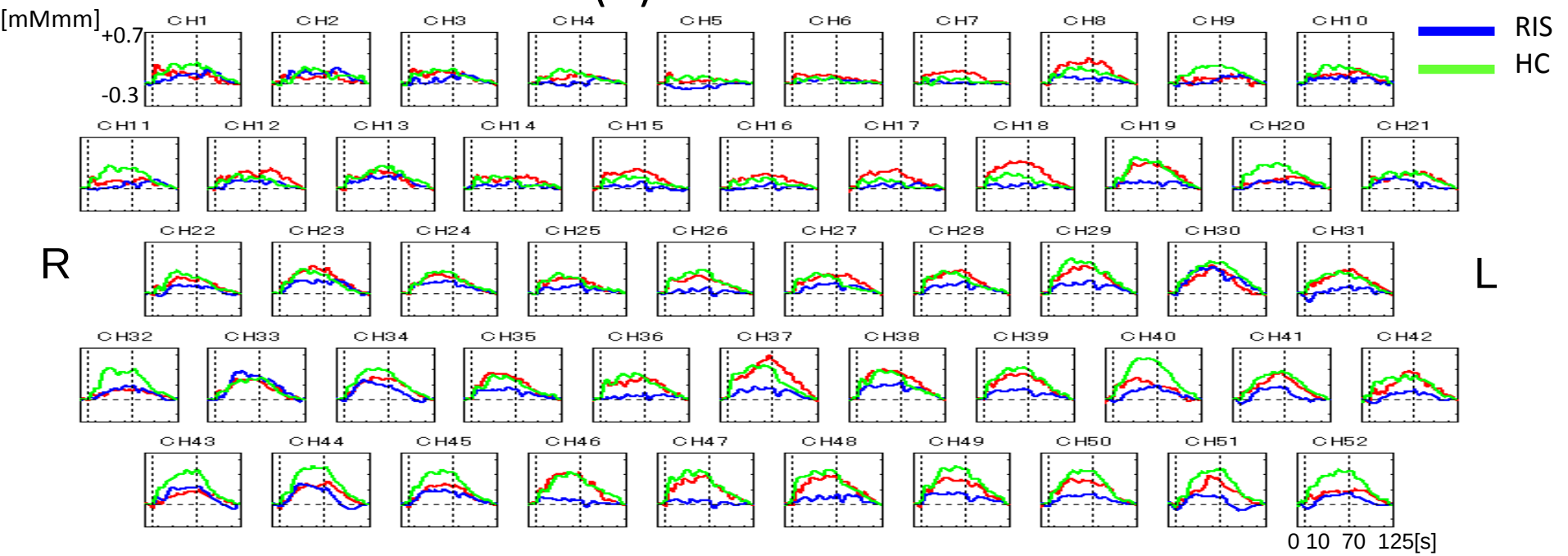
(B) Mean oxy-Hb increase in CH46



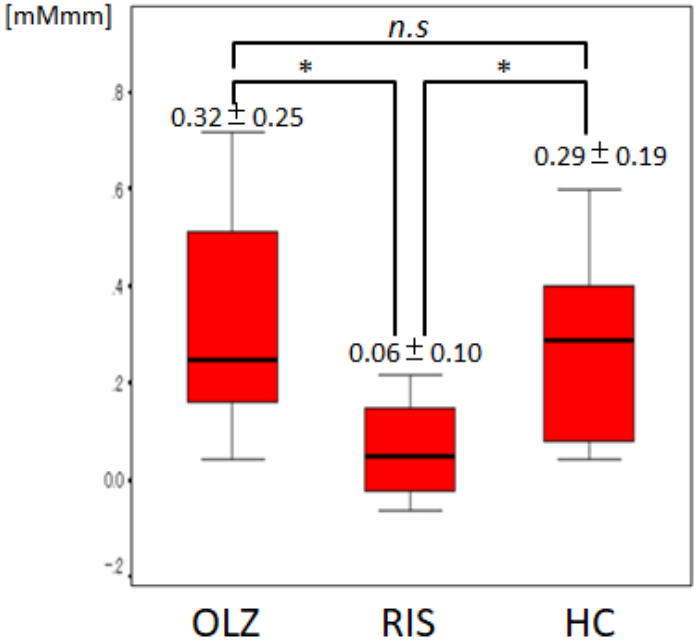
Dunn's test

* P<0.05

(A) OLZ vs RIS vs HC



(B) Mean oxy-Hb increase in CH46



Dunn's test

* P<0.05

Table 1

Characteristics	OLZ group (*n*=10)	RIS group (*n*=10)	Control group (*n*=10)	*P*[a]
Age, years: mean (SD)	26.7 (7.6)	29.7 (8.6)	29.5 (8.5)	0.274
Gender, men/women: n	6 / 4	3 / 7	5 / 5	0.392
Education (years)	12.1(1.7)	11.4 (1.3)		0.33
Illness duration (years)	6.1 (4.6)	8.6 (7.2)	N/A	0.42
PANSS, mean (SD)				
Total	55.6 (20.7)	52.8 (11.0)	N/A	0.71
Positive	14.3 (7.4)	12 (7.2)	N/A	0.94
Negative	13.2 (4.7)	15 (5.5)	N/A	0.54
Antipsychotic dosage[b], mg/day: mean (SD)	460 (248)	280 (120)	N/A	0.072
Task performance, mean (SD)	11.6 (6.9)	11.1 (4.1)	15.8 (4.9)	0.12

N/A, not applicable

a. One-way ANOVA was used to test the difference in age and task performance across the three groups. Chi-square test was used to test the difference in gender across the three groups. Two sample *t*-test was used to compare the differences in PANSS Total and CP equivalent. The Mann-Whitney *U* test was used to compare the Education years, Illness duration, PANSS Positive and Negative score.

b. Antipsychotic dosages are reported as chlorpromazine equivalents calculated based clinically equivalent dosing estimates.