Characteristics of Cortical Activation in Schizophrenia during the Card Game “Concentration”

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Summary: Various functional imaging studies have demonstrated reduced lateralization of cortical activation during neurocognitive tasks in schizophrenia. –A well-known card game, “concentration”, reflects working memory (WM). We compared characteristics of hemodynamic changes in the prefrontal to temporo-parietal areas of the brain during this card game between 24 outpatients with schizophrenia and 24 age- and gender-matched healthy control subjects. Using multi-channel near-infrared spectroscopy, we measured relative changes in oxygenated hemoglobin concentration (oxy-Hb changes), which reflects brain activity during this task. Patients showed reduced lateralization in the midfrontal area, which is involved in executive functions, and in the inferior parietal area, involved in WM subcomponents. We also found a significant negative correlation between left midfrontal region oxy-Hb changes and severity of negative symptoms of schizophrenia. Our results characterized disease-related features, suggesting the usefulness of oxy-Hb change measurement during this card game for assessing functional outcome in schizophrenic patients.

Key words card game “concentration”, multi-channel near-infrared spectroscopy, reduced lateralization, schizophrenia, working memory

INTRODUCTION

The card game “concentration” (also known as “matching pairs” or “pelmanism”) involves turning over pairs of cards with the aim of locating cards with matching numbers. This requires players to retain information about cards and manipulate the stored information. Jimison et al. [1] used this card game as a tool for measuring working memory (WM). WM is a limited-capacity system involved in temporary storage and manipulation of information [2]. This activity is a high-order cognitive function that is essential to daily life. Much is known about WM deficits in

patients with schizophrenia, which have been shown to persist even when clinical symptoms decrease, and they are suggested to be important for their clinical outcome [3-6]. Previous studies have demonstrated reduced lateralization of activation during WM tasks [7-9] and correlation between degree of WM impairment and negative symptoms in schizophrenic patients [4, 10].

Tupak et al. [11] revealed lateralization of activation during a semantic verbal fluency task in healthy subjects. Lee et al. [7] demonstrated reduced lateralization during a spatial WM task in patients with schizophrenia, suggesting that this finding might be the re-

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Abbreviations: ANOVA, analysis of variance; ATMT, advanced trail-making test; BA, Brodmann's area; fMRI, functional magnetic resonance imaging; HPD, haloperidol; ICD-10, International Classification of Diseases, tenth revision; IQ, intelligence quotient; JART, Japanese version of the National Adult Reading Test; NIRS, near-infrared spectroscopy; PANSS, positive and negative syndrome scale; PLSD, protected least significant difference; ROI, region of interest; SD, standard deviation; WM, working memory.

sult of a compensatory mechanism for WM dysfunction. As this dysfunction is shown throughout the various stages of illness, it is important to detect it early. In addition to increased activation of the right parietal cortex during visuospatial maintenance in schizophrenia, Henseler et al. [12] (2009) reported that more severely affected patients had stronger prefrontal activation and poorer performance.

We have explored neuroimaging methods using an easy and inexpensive visuospatial WM task to investigate characteristics of schizophrenia. In this study, we compared hemodynamic changes between healthy subjects and patients while actually playing cards on a table. The game is well known and has simple rules. Therefore, it may be an appropriate neurocognitive model for measuring cortical activity enhancement during WM tasks encountered in daily life.

Near-infrared spectroscopy (NIRS) is a practical, noninvasive imaging method employing scattered near-infrared light to measure changes in oxygenated blood hemoglobin at the surface of the brain. The underlying principle is that relative changes in oxygenated hemoglobin concentration (oxy-Hb changes) reflect regional cerebral blood volume, which is associated with brain activity. NIRS has been increasingly used to investigate schizophrenia because the apparatus is relatively small and portable, is easily set up, and imposes minimal limitation of movement [13-18]. However, most NIRS studies during WM tasks have focused on frontal areas [14-18]; specific findings in other cortical areas have been unclear.

In this study, we measured oxy-Hb changes during the card game “concentration” using multi-channel

NIRS covering the prefrontal to temporo-parietal areas to investigate characteristics of schizophrenia. The primary aim of the present study was to determine using NIRS whether the card game “concentration” was useful as a neurocognitive task and to identify dissociated activity patterns in patients with schizophrenia compared with those in healthy subjects during this task. We hypothesized that there would be reduced lateralization of activity in patients, as in previous studies. An additional aim was to investigate the relationships between functional brain activity and psychiatric symptoms.

METHODS

Participants

Study patients included 24 Japanese outpatients with schizophrenia (15 male and 9 female; mean age, 30.0 ± 6.0 years) and 24 age- and gender-matched healthy control subjects (15 male and 9 female; mean age, 29.0 ± 4.4 years). Two attending psychiatrists diagnosed patients using the International Classification of Disease, tenth revision (ICD-10) [19]. All subjects were right-handed according to the Edinburgh Inventory [20]. Their mean intelligence quotient (IQ) values were evaluated by the Japanese version of the National Adult Reading Test (JART) [21]. No subject had any history of neurologic disorder, substance abuse, alcohol abuse, seizure, or head injury. Healthy control subjects had no history of psychiatric illness or familial history of psychosis. All patients were taking atypical antipsychotic medications (i.e. olanzapine (n=8), risperidone (n=7), aripiprazole (n=3), quetiap-

TABLE 1.
Subject characteristics

	Patients	Controls	p value
Age (year)	30.0 ± 6.0	29.0 ± 4.4	0.48
Gender (F/M)	9/15	9/15	
Education (year)	13.3 ± 1.5	16.5 ± 1.2	$<0.01^*$
IQ	100.3 ± 10.1	106.2 ± 6.1	0.07
Illness Duration (year)	5.1 ± 2.6		
PANSS score			
Positive subscale	20.7 ± 2.9		
Negative subscale	19.7 ± 3.6		
Total	45.0 ± 4.4		
Medication			
HPD equivalent (mg/day)	6.0 ± 2.8		

Data are presented as means $\pm$ SD. $p < 0.05$, comparing patients with controls.
Abbreviation: HPD, haloperidol.

ine (n=2), perospirone (n=2), blonanserin (n=2). The mean daily antipsychotic dose in terms of haloperidol (HPD) equivalent was 6.0 ± 2.8 mg [22]. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) [23]. Neither patients nor control subjects showed visual disabilities. The ethics committee of Kurume University approved the present study. Written informed consent was obtained from all subjects prior to participation in the study. Demographic and clinical characteristics of all subjects are shown in Table 1.

Measures

NIRS measurement

Oxy-Hb changes, which were calculated from the difference in absorbance based on the modified Beer-Lambert law, were measured during tasks using a multi-channel NIRS machine (ETG4000; Hitachi, Tokyo) from 22 left- and 22 right-sided channels (total, 44) [24]. Distances between the injector and the detector probe were 3 cm. We defined each measurement area between probes as a channel (ch). The NIRS machine is thought to measure changes at points 2 to 3 cm beneath the scalp, that is, the cerebral cortical surface [25,26]. The lowest anterior probes, right ch 22

and left ch 19, were positioned along the Fp1-Fp2 line according to the International 10-20 system used in electroencephalography (Fig. 1a). In the present study, all subjects were instructed to minimize their movements and jaw fixation was used during the task to avoid movement artifacts. NIRS data were calculated from the mean waves of oxy-Hb changes at each recording site and region of interests (ROIs), which corresponded to presumed sites of WM function. ROIs evaluated to determine physiologic significance were selected for channels reflecting the midfrontal area and inferior parietal area. The midfrontal area has been reported to reflect executive function, and the inferior parietal area to reflect verbal and visuospatial WM [27-29]. The pre-task baseline was determined as the mean during the 10 sec preceding the task period, while the post-task baseline was determined as the mean during the 30-40 sec after the task period. Linear fitting was applied to the data between these two baselines.

Right-hand motion task

As an initial study, we investigated a right-hand motion task to confirm the relationship between activation region and anatomic region. Twenty-four right-

Fig. 1. Study design: a, Location of channels: b, protocol. Each subject performed one session, consisting of five blocks and tried to make six pairs during the 30 sec task period. They played the "concentration" game using cards actually on a table. When the control period was finished, we put out 12 cards (6 pairs) arranged face down at random, and when task period was finished, we put out 12 identical cards (aces). There was a start signal when the new 12 cards were put out.

handed healthy control subjects participated in the activation task. In the right-hand motion task, 12 cards bearing the same number (ace) were arranged on the table, and subjects were instructed to repeat turning them face up and turning them face down for 2 cards in order, using only the right hand. As a control condition, all subjects were asked to relax with their eyes open and their hands still. Averaged waveforms for 5 of these blocks were measured as one session, and oxy-Hb changes from the control condition were expressed numerically for each 100 milliseconds, and the area of the task period (30 sec) was calculated as data.

Activation task

Brain activation was measured during the card game “concentration”. For the activation task, each subject sat on a comfortable chair and had to perform the task using actual playing cards on a table. They were instructed to use only the right hand. One session consisted of 2 contrasting conditions (concentration task, control condition), and all subjects alternated between these conditions. The concentration task was performed as 5 blocks in 1 session. In the concentration task, subjects searched for identically numbered card pairs among 12 cards placed face down in front of them. Subjects were instructed to select matching numbers irrespective of color, suit, or other markings. In the control condition, 12 cards bearing the same number (ace) were used, and subjects were instructed to repeat turning them face up and turning them face down for 2 cards in order. According to different time windows for control and task conditions, the control period took more than 30 sec to recovery of activation. Therefore, we set the control period at 50 sec in order to ensure sufficient recovery time. Averaged waveforms for 5 blocks were analyzed as 1 session using the “Integral mode” of the machine. Oxy-Hb changes between activation and control periods were expressed numerically for each 100 milliseconds. The area of the task period (30 sec) was calculated (Fig. 1b). We used values from this area as our NIRS data. The total number of cards paired was used as the performance for a session.

Relationship between recording site and anatomic region

We investigated the right-hand motion task during NIRS to confirm each channel of ROI. NIRS data were converted to a normalized brain image template (3 dimensional composition indication unit: Hitachi, Tokyo). In the right-hand motion task, oxy-Hb change at all left recording sites was 13.4 ± 24.3 mmol*mm

and that at all right recording sites was 8.2 ± 25.3 mmol*mm. Significant differences were obtained between the left ch 3 and the right ch 2 ($F=7.62$, $p<0.01$), and between the left ch 8 and the right ch 6 ($F=4.77$, $p<0.04$). Oxy-Hb changes at each of these left channels (left ch 3, left ch 8) were significantly larger than those at the corresponding right channel (right ch 2, right ch 6, respectively). Since these left channels were thought to be associated with neural activity in the left motor cortex due to right-hand motion, ROIs reflecting the midfrontal area and inferior parietal area were speculated to be left ch 11 and right ch 12, and left ch 13 and right ch 10, respectively.

Statistical analysis

Mean data from each group were used in the analysis (healthy subjects; $n=24$, patients; $n=24$). NIRS data were examined using three-way analysis of variance (ANOVA) (group $\times$ hemisphere $\times$ recording sites) to evaluate the group main effects. Whether interaction was obtained or not, two-way ANOVA (group $\times$ hemisphere) was evaluated in all recording sites and ROIs. Finally, whether interaction was obtained or not, one-way ANOVA (group) was evaluated by hemisphere or for all recording sites and ROIs. Furthermore, one-way ANOVA (hemisphere) was evaluated in groups or all recording sites and ROIs. Fisher’s protected least significant difference (PLSD) was then applied as a post hoc test between sites or groups. The correlation between the oxy-Hb changes and the PANSS score is expressed as Pearson’s product-moment correlation coefficient; Bartlett’s test was used to evaluate statistical significance. A value of $p<0.05$ was accepted as statistically significant. Values are expressed as the mean $\pm$ standard deviation (SD). We used the oxy-Hb changes as data in this study because these changes correlate more strongly with BOLD of functional magnetic resonance imaging (fMRI) than do deoxy-Hb changes [30].

RESULTS

Performance on “concentration” game task

Task performance was 18.8 ± 4.3 in patients and 21.9 ± 6.6 in controls, showing no significant difference between groups ($F=3.65$, $p>0.06$) (Table 2).

“Concentration” game task

Oxy-Hb change at all left recording sites was 9.30 ± 20.2 mmol*mm and that at all right recording sites was 10.0 ± 22.8 mmol*mm during the game task in patients, compared with 23.5 ± 35.3 mmol*mm and

25.0±33.1 mmol*mm in controls, respectively. In all recording sites, three-way ANOVA (group × hemisphere × recording sites) revealed a significant main effect of 'group' ($F=147$, $p<0.01$), but no significant interactions. Two-way ANOVA (group × hemisphere) revealed a significant main effect of 'group' ($F=137$, $p<0.01$), but no significant interactions. One-way ANOVA revealed significantly smaller values for patients than for controls on both sides (left, $F=64.1$, $p<0.01$; right, $F=72.6$, $p<0.01$). No significant lateralization of oxy-Hb changes at any recording site was observed in either group (controls, $p=0.50$; patients, $p=0.60$).

In ROI, three-way ANOVA (group × hemisphere × recording sites) revealed a significant main effect of 'group' ($F=29.8$, $p<0.01$) as well as significant interactions of 'group × hemisphere × recording sites' ($F=9.80$, $p<0.02$). Oxy-Hb change at left ch 11 was 6.90±14.7 mmol*mm and that at right ch 12 was

12.4±21.5 mmol*mm in patients. In controls, oxy-Hb change at left ch 11 was 36.7±27.9 mmol*mm; at right ch 12, this was 21.1±16.6 mmol*mm (Table 2). In left ch 11 and right ch 12, two-way ANOVA (group × hemisphere) revealed a significant main effect of 'group' ($F=20.5$, $p<0.01$) as well as a significant interaction of 'group × hemisphere' ($F=6.16$, $p=0.01$). One-way ANOVA revealed that oxy-Hb changes at left ch 11 were significantly larger than those at right ch 12 in controls ($F=5.52$, $p=0.02$), but no significant difference was found in patients ($F=1.07$, $p=0.31$). In addition, oxy-Hb changes at left ch 11 in controls were significantly larger than in patients ($F=21.4$, $p<0.01$), but no significant difference was found between groups at right ch 12 ($F=2.45$, $p=0.12$) (Fig. 2).

Oxy-Hb change in patients at left ch 13 was 12.6±23.0 mmol*mm; at right ch 10, this was 12.3±23.6 mmol*mm. In controls, oxy-Hb change at left ch 13 was 21.4±31.8 mmol*mm, while at right ch 10, this was 41.2±29.6 mmol*mm (Table 2). In left ch 13 and right ch 10, two-way ANOVA (group × hemisphere) revealed a significant main effect of 'group' ($F=11.1$, $p<0.01$) as well as a significant interaction of 'group × hemisphere' ($F=3.99$, $p<0.05$). One-way ANOVA revealed that oxy-Hb changes at left ch 13 were significantly smaller than those at right ch 10 in controls ($F=5.02$, $p=0.03$), but no significant difference was found in patients ($F=0.001$, $p=0.97$). In addition, oxy-Hb changes at right ch 10 in controls were significantly larger than in patients ($F=14.0$, $p<0.01$), but no significant difference between groups was found at left ch 13 ($F=1.20$, $p=0.28$) (Fig. 3).

TABLE 2.

Comparison between "concentration" task results in patients with schizophrenia and healthy subjects

	Patients (n=24)		Controls (n=24)	
	Mean	SD	Mean	SD
Performance	18.8	4.3	21.9	6.6
Oxy-Hb change [mmol*mm]				
Left ch 11	6.9	14.7	36.7	27.9
Right ch 12	12.4	21.5	21.1	16.6
Left ch 13	12.6	23.0	21.4	31.8
Right ch 10	12.3	23.6	41.2	29.6

Fig. 2. Oxy-Hb changes appear along the ordinate and groups along the abscissa. Oxy-Hb changes at left ch 11 in patients (□) were significantly smaller than in healthy controls (■). Oxy-Hb changes at left ch 11 were significantly larger than those at right ch 12 in controls, but not in patients.

Fig. 3. Oxy-Hb changes appear along the ordinate and groups along the abscissa. Oxy-Hb changes at right ch 10 in patients (□) were significantly smaller than in healthy controls (■). Oxy-Hb changes at right ch 10 were significantly larger than those at left ch 13 in controls, but not in patients.

Fig. 4. Relationship between oxy-Hb changes and negative symptom scores.

Oxy-Hb changes at left ch 11 showed a significant negative correlation with negative symptom scores in patients. The correlation coefficient (r) was -0.43 ($p=0.03$) at left ch 11.

Relationship between oxy-Hb changes and PANSS scores

Oxy-Hb changes at left ch 11 showed a significant negative correlation with negative symptom scores in patients. The correlation coefficient was -0.43 ($p=0.03$) at left ch 11 (Fig. 4). On the other hand, oxy-Hb changes did not correlate with positive symptom scores, total symptom scores, or antipsychotic drug dose. Moreover, oxy-Hb changes were not correlated with performance in either group.

DISCUSSION

This study compared regional oxy-Hb changes between patients with schizophrenia and healthy control subjects during a task involving the card game “concentration”. This task requires attention and executive control, and it is considered to involve WM. Recent neuroimaging studies during neurocognitive tasks have examined anatomic regions related to WM functions, suggesting that the phonologic loop involved in WM is associated mainly with the left inferior parietal region {Brodmann’s area (BA) 40} and Broca’s area (BA 6/44) [27,31,32], while the visuospatial sketchpad in WM is associated mainly with the right inferior parietal region (BA 40), premotor cortex (BA 6), inferior frontal cortex (BA 47), and visual association area (BA 19) [27,31,32]. The central executive system is considered to involve mainly left and right dorsolateral prefrontal areas (BA 9/46) [33]. Thus, the mid-

frontal area has been thought to reflect executive function, and the inferior parietal area to reflect both verbal and visuospatial WM in common.

In the present study, we first investigated the relationship between anatomic region and channel, using a right-hand motion task. The left motor cortex was associated with right-hand motion, specifically around ch 3 and ch 8, corresponding to BA 4. Therefore, left ch 11 and right ch 12 corresponded to the midfrontal area including BA 9/46. Left ch 13 and right ch 10 represented the inferior parietal area, including BA 40. In previous studies, reduced lateralization of activation during WM tasks was reported in patients with schizophrenia [6-8]. This finding suggests reduced WM in patients [9]. Nakahachi et al. [14] (2010) evaluated working memory using the advanced trail-making test (ATMT) in healthy subjects, and observed bilateral activities during ATMT task F [14]. In the present study, reduced lateralization at all recording sites was observed in both groups. This finding is thought to reflect use of not only visual but also verbal information in the task, as also occurs during ATMT task F. The various other features of the card gave clues for memorizing the card’s position, which may have reflected functions including verbal working memory.

Regarding the ROI in the area assumed to be the midfrontal region (left ch 11, right ch 12), oxy-Hb changes at the left recording site were significantly greater in controls than in patients. Oxy-Hb changes at left ch 11 were significantly greater than those at right ch 12 in controls, while no laterality was observed in patients, which may have reflected schizophrenia-associated reduction of executive function. In the area taken to be the inferior parietal region (left ch 13 and right ch 10), oxy-Hb changes at the right recording site were significantly greater in controls than in patients. Oxy-Hb changes at right ch 10 were significantly greater than those at left ch 13 in controls, while no laterality was observed in patients. The inferior parietal region is related to verbal and visual working memory [27,31]. However, in the present task, we suspected that healthy subjects showed right hemisphere predominance because visuospatial information retention was more important than verbal information, while patients showed reduced lateralization because of visuospatial and verbal WM deficits in comparison with controls. Our examination showed reduced lateralization of activation at ROIs, while performance did not differ significantly between groups. This finding may reflect WM deficits and possibly also compensation for cortical dysfunction, as suggested in a previous report [7].

In previous studies, a correlation was observed between WM in patients and the negative symptom assessment score [4,10]. Meanwhile, WM deficits have been proposed as a functional marker of schizophrenia [34,35]. In our study, although there was no correlation between performance and any subcomponent of PANSS score, a negative correlation was observed between negative symptom assessment score and oxy-Hb changes at left ch 11. That is, patients with more severe negative symptoms have weaker activation of the area reflecting executive function. Our finding suggests that deficient local blood flow changes at left ch 11 may serve as a biologic marker of schizophrenia. Although further studies are necessary, this marker might serve as a simple, objective evaluation tool, providing a useful way to predict social functions, and to decide when to introduce rehabilitation. However, our study had several limitations: 1) Education years were not controlled. Although our data showed no significant difference between education and performance or activation, we believe that future studies should take this issue into account. 2) Anatomic region. It is assumed that the spatial resolution of the NIRS is poor. We performed a right-hand motion task and speculated on the relationship between anatomic region and channel from activation of right-hand movement. However, our NIRS data were not analyzed in terms of individual MRI brain scans. 3) Body movement. NIRS does not restrict body movement and can be applied in a natural posture, but artifacts are likely to be produced by nodding and rotation of the head. We therefore employed jaw fixation and data averaging to reduce artifacts as much as possible. 4) Influences of medications. All patients received atypical anti-psychotic drugs, with which WM deficits have been associated [36,37]. However, WM deficits have been reported in untreated patients with schizophrenia, in patients about to begin treatment, and in patients at clinical onset of schizophrenia, as well as in healthy first-degree relatives of patients with schizophrenia [4,35,38,39]. The relationship between medication effects and WM is unclear. Future studies should investigate drug-naïve patients.

CONCLUSION

To our knowledge, this is the first study to perform NIRS during tasks associated with the card game “concentration”. This study showed reduced lateralization of activation in the midfrontal area and the inferior parietal area in patients with schizophrenia. We suggest that these findings may be disease-related features.

Thus, this actual playing card game is useful as a neuropsychological task. In addition, an observed relationship between oxy-Hb changes and negative symptom scores may be of help in measuring and predicting functional outcome in patients.

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