Comparison of changes in the oxygenated hemoglobin level during a “Modified rock-paper-scissors task” between healthy subjects and patients with schizophrenia

Cognitive dysfunction in Schizophrenia

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Aim

The purpose of this study, using single-event-related near-infrared spectroscopy (NIRS), was to examine the psychophysiological and social function assessment of 30 schizophrenic patients during a modified rock-paper-scissors (mRPS) task.

Methods

We set up a screen in front of the subjects, on which pictures of a rock, paper, and scissors were randomly presented. Subjects were asked to give verbal answers under the conditions of win, lose and draw respectively. Using the 44-channel NIRS system, we evaluated the maximum amplitude of oxygenated hemoglobin (oxy-Hb), latency, and the area based on the arithmetic mean of resulting values after the task between 30 out-patients with schizophrenia and 30 healthy subjects, and analyzed the frontal pole area, dorsolateral prefrontal region, and parietal association area as regions of interest (ROI).

Results

In schizophrenic patients, oxy-Hb changes (Δoxy-Hb) when losing the task showed a significantly lower level of Δoxy-Hb of ROI than in the controls. In addition, a significant positive correlation was observed between the Global Assessment of Functioning scale (GAF) and Δoxy-Hb in ROI, and a significant

negative correlation was observed between the negative symptom rating scale of PANSS and Δoxy-Hb in ROI.

Conclusion

From these results, we conclude that Δoxy-Hb levels when performing the mRPS task assessed using NIRS may be a useful psychophysiological marker to evaluate the cognitive and social functions of schizophrenic patients.

Keywords

Near-infrared spectroscopy, Rock-paper-scissors task, Schizophrenia, Social function, Working memory

This trial was registered with the ethical committee of Kurume University (no. 10086).

Introduction

Rock-paper-scissors (RPS) is a very popular game in which the winner and loser are decided based on hand movements, and can be played over a wide age range from children to adults. There are three hand movements (rock, paper and scissors), and the winner and loser are decided based on these movements: Rock wins against scissors, but loses against paper because it cannot be cut by scissors, but can be wrapped in paper. Similarly, scissors win against paper and lose against rock, and paper wins against rock and loses against scissors. The opponent's hands are simultaneously extended when calling out. [1] This game is widely performed worldwide and is known as rock-paper-scissors (or scissors-paper-stone) in the English-speaking world. Thus, it is termed RPS in this report.

A delay in showing a hand command after confirming the command of the opponent is generally regarded as cheating. Such modified rock-paper-scissors (mRPS) is also performed using three commands (win, lose and draw). The subjects must perform the task while recognizing what the presented hand is. For this, attention, an executive function based on the memory of the presented hand is important, and working memory (WM) [2] should be considered. WM is the function of retaining information and achieving tasks while recalling learned knowledge and experience from memory. In addition, WM was reported to be involved in functions of focused attention and switching attention, has been proposed to support goal-oriented behavior [3,4] and is considered the main function necessary to perform mRPS. Furthermore, as an important characteristic of this mRPS, the practitioner can control the result of the game. Therefore, depending on which result the practitioner selects, a different cognitive psychological process is activated. For example, when selecting a win, although the practitioner presents their hand according to the desire to try

to win as well as the normal RPS, when selecting lose, they have to present their hand while resisting their desire to win. In the case of a draw, the simple strategy is to copy the hand that has been presented, although they have to control their desire and behavior.

In previous studies using mRPS, Matsubara et al. [5] suggested the difficulty of actively losing when the desire is to win, and reported an association between cognitive conflict and inhibitory function. Furthermore, it was verified that mRPS is associated with an increase of cerebral blood flow in the prefrontal cortex using NIRS, and some theorists argue that an impaired ability to play mRPS is a useful tool for assessing the frontal lobe function. [1,6,7] Kikuchi et al. [6] who investigated brain activity during mRPS performance in healthy people using NIRS for the first time, reported that modified lose RPS leads to greater activation of the dorsolateral prefrontal region than modified win RPS. The brain function during mRPS in healthy people in past studies using functional MRI showed a significant increase in activity in the medial frontal gyrus (BA 10), left ventrolateral frontal gyrus (BA 11/47), and left pallidum under the win condition, [8] bilateral supplementary motor area under the draw condition [9] and inferior frontal gyrus and left supplementary motor area (SMA) under the lose condition.[10] In this way, mRPS activates a wide range of activities in the cognitive task area and motion-related area of the frontal lobe. Furthermore, in recent years, mRPS has sometimes been applied in clinical practice, such as severity assessment of cognitive impairment in patients with depression [11] and rehabilitation due to frontal lobe injuries or in elderly people with dementia. [12]

On the other hand, schizophrenia widely affects higher brain functions such as the attention function, executive function, monitoring, memory and language. As a result, patients suffer disadvantages in daily life. It is thought that the

impairment causes social dysfunction, and that this is closely associated with the function of the PFC. [13,14] Moreover, based on several cognitive tasks that activated the frontal lobe, schizophrenia was reported to be related to dysfunction of the PFC, encompassing the sites of executive function and WM. [15,16,17] Takizawa et al. [18] reported the results of a comparison between schizophrenia patients and a healthy group regarding the frontal lobe function during a verbal fluency task using multi-channel NIRS; in schizophrenia, changes in oxygenated hemoglobin were inefficient, and this was consistent with the results of Suto et al. [19] Thus, schizophrenia is considered to impair the frontal lobe function and prefrontal area-parietal network of WM. Therefore, further clarification of this feature may contribute to the pathological assessment of schizophrenia. In addition, it has been reported that the WM failure of schizophrenia is more prominent in the visuo-spatial WM than verbal WM. [20] We selected mRPS, one of the visual and inhibitory tasks, as a challenge as, to our knowledge, no studies have evaluated the psychophysiological effect of schizophrenia using mRPS in detail. In this study, using single-event-related near-infrared spectroscopy, we investigated the psychophysiology and social function of schizophrenic patients, and clarified activated brain areas during mRPS tasks.

Method

Subjects

The study subjects included 30 Japanese out-patients who visited Kurume University Hospital, and were given a diagnosis of schizophrenia (22 paranoid type, 8 non-paranoid type, 15 females and 15 males; mean age, 33.6 ± 8.5 years) by two trained psychiatrists based on the International Classification of

Disease, tenth revision (ICD-10) [21], and the same number of age-matched healthy control subjects (16 females and 14 males; mean age, 31.6 ± 8.5 years). The patients were recruited during the 3 years from 2013 to 2016 based on consecutive referrals. All were native Japanese speakers, and were right-handed according to the Edinburgh Handedness Inventory. [22] All of the patients were taking atypical antipsychotics (i.e. risperidone [n=20], olanzapine [n=10]). The mean daily dosage of antipsychotic drugs in terms of the risperidone equivalent was 4.4 ± 1.3 mg. Their mean intelligence quotient values were evaluated using the Japanese version of the National Adult Reading Test. [23] The exclusion criteria were: comorbid neurological illness, a history of previous traumatic head injuries, seizures, substance and alcohol abuse, dementia, and anemia. Healthy control subjects had no history of mental illness. In addition, visual impairment was not observed in either group. Psychiatric symptoms and the social function of patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) [24] and the Global Assessment of Functioning (GAF) scale (Diagnostic and Statistical Manual of Mental Disorders, Ⅳ Edition, Text Revision) [25] on the same day as measurement by NIRS. Demographic and clinical characteristics of all subjects are shown in Table 1. We informed all subjects of the study in written form, and obtained their consent. The study was performed with the approval of the ethical committee of Kurume University (No.10086).

NIRS measurement

In recent NIRS studies, the activity of oxy-Hb was used as an indicator of the hemodynamic response rather than deoxy-Hb; in the present study, we used oxy-Hb as an indicator of cerebral activation. [26, 27] We measured relative

changes in oxy-Hb (Δoxy-Hb) during the task, which were calculated from the difference in light absorption characteristics based on the modified Beer-Lambert law, using the 44-channel NIRS system (ETG-4000, Hitachi Medical Co.). The distance between the injector and detection probe was 3 cm, and we defined the midpoint as the channel (ch). When near-infrared light characterized by a high bio-permeability was projected from the scalp, it was considered to reach the cerebral cortex located approximately 2-3 cm deep. [28] The probes were placed on the frontotemporal region of the subjects, and the most anteroinferior channels were located on the line connecting the T3-Fp1-FPZ-Fp2-T4 line in the International 10-20 system for electroencephalography. [29] During the NIRS measurement, the jaw of subjects was lightly fixed using a chin stand to minimize movement artifacts. For NIRS measurement, we measured the whole recording unit, and established three areas as regions of interest (ROI): the frontal pole area (left ch 19 and right ch 22), the dorsolateral frontal lobe region (DLPFC; left ch 11 and right ch 12), and the anterior and middle 9parietal lobe regions equivalent to the parietal association area (left ch 9 and right ch 5), since the prefrontal-parietal network is considered to be important for WM associated with visual stimuli (Figure 1). In addition, the probe position was decided based on the association between the channel at which changes in the oxy-Hb level were observed during a right finger movement task and the anatomical region: The right finger movement task [30] was correlated with the left motor cortex, and the channel corresponding to Brodmann area (BA) 4 was defined as a region near ch 3 and ch 8, based on which the middle frontal region, including the dorsolateral prefrontal area (BA9/46), was considered to be correlated with left ch 11 and right ch 12. And we performed the finger movement task in all cases. With reference to our previous study, [17, 31] the pre-task baseline was set to 1 second before presenting the stimulus, and the

post-task baseline was set to a period of 11 seconds from 10 seconds after the stimulus presentation. Linear fitting was applied to the data between these two baselines. For each channel relationship with the anatomical region, NIRS data were converted to a normalized brain image template (three-dimensional composition indication unit; Hitachi).

Task design

We selected mRPS as a cognitive task, and the brain activity was measured during task performance. As a method of NIRS measurement, we chose a single-event-related design. This is a method to apply short stimulations one by one in a control state, and multiple and weak stimulations are required compared with the block design. [32] Although it removes artifacts on analysis, there is a merit in that waveforms can be precisely analyzed one by one, and it is considered to be able to capture brain activity more sensitively. Each subject performed the task while sitting on a chair in the examination room, which blocked sounds or unnecessary visual stimuli. We set up a screen in front of the subjects, on which pictures of a rock, paper, and scissors were randomly presented. In the resting condition, they were instructed to continuously gaze at a black dot on the monitor for 12 seconds, and required to say “A- I- U- E- O (in Japanese)” repeatedly. During the mRPS task, they were instructed to verbally respond with one of the three choices (i.e., rock, paper, or scissors) as soon as possible when they saw a picture presented on the monitor for 0.3 seconds as a stimulus. The task consisted of three types of condition (win, draw and lose), and the subject was exposed to each condition 20 times. Specifically, in the win condition, when the “rock” was presented, the subjects answered “paper” immediately, in the same way as “paper” with “scissors”, and “scissors” with

“rock”. Draw and lose conditions were also examined in the same way. In addition, in order to prevent any effect of the task presentation order, each condition was performed randomly. The task design is shown in Figure 2.

In data analysis, the maximum amplitude, latency, and area were determined referring to the event-related potential employed by Shoji et al. [33] To reduce variation among one-word stimulations, single stimulation was loaded 20 times, and data were determined from the averaged waveform of 20 stimulations, similarly to analysis of the p300 component of the event-related potential. However, since variation of this event-related potential is large between and within individuals, it is necessary to set a time limit and analyze the area to achieve reproducibility. Thus, the time limit was set as the time to the mean maximum amplitude from stimulus presentation, and the approximate value of the area was used as an analytical element. In a pilot study, the maximum latency after stimulus presentation was 5.6 ± 0.58 seconds in healthy subjects. Based on this, each 100-millisecond increment over the 6 seconds period after stimulus presentation was determined and regarded as Δoxy-Hb.

Statistical analysis

For statistical analysis, two-way layout analysis of variance (two-way ANOVA) with the tasks was performed between each ROI and each group or diagnosis and task condition. A significance level below 5% was regarded as significant in two-way layout analysis of variance. For multiple comparison, the Bonferroni/Dunn method was used for evaluation among tasks in each group, and values below 1.67 (5/3) % after correction with multiple comparison were regarded as significant. The correlation between Δoxy-Hb and the PANSS score/GAF score is expressed as the Pearson’s product-moment correlation

coefficient with reference to Takei's study [34]. As statistical analysis software, Stat View. 5.0 (SAS Institute, Cary, NC, USA) was used. The data of subjects with a mRPS success rate exceeding 80% in all tasks were included in analysis.

Results

Task performances

To compare performance differences, we compared the success rate of each group's tasks. During the win condition, task performance was 20 ± 0 in healthy subjects and 19.93 ± 0.25 in patients ($F = 2.071$, $P > 0.05$). During the draw condition, task performance was 19.76 ± 0.50 in healthy subjects and 19.66 ± 0.61 in patients ($F = 0.482$, $P > 0.05$). During the lose condition, task performance was 19.66 ± 0.48 in healthy subjects and 19.33 ± 0.92 in patients ($F = 3.085$, $P > 0.05$). All subjects had a response rate above 80%. There were no significant differences between healthy subjects and the patient group during the 3 conditions.

Activation of ROI during mRPS tasks

In the frontal pole region

In the mRPS task, two-way ANOVA revealed a significant main effect of "group" in the following ch, but no significant interactions. The area of Δoxy-Hb in patients was significantly smaller than in the control group when the assigned criterion was to lose (left ch 19 ($F = 22.933$, $P < 0.0001$), right ch 22 ($F = 15.088$, $P = 0.0003$)). In the control group, there were significant differences between the conditions (left ch 19; lose versus win ($P < 0.0001$), lose versus

draw (P < 0.0001), right ch 22; lose difference win (P < 0.0001), lose versus draw (P < 0.0001)). The maximum amplitude was significantly higher in the control group than in the patient group when the assigned criterion was to lose (left ch 19 (F = 9.660, P = 0.0029), right ch 22 (F = 8.804, P = 0.0043)). In the control group, there were significant differences between the conditions (left ch 19: lose versus win (P < 0.0001), lose versus draw (P < 0.0001), right ch 22: lose versus win (P < 0.0001), lose versus draw (P < 0.0001). The latency time was significantly shorter in the control group than in the patient group for left ch 19 when the assigned criterion was to lose (F=6.732, P = 0.0119). At right ch 22, the latency time of the control group was significantly shorter than in the patient group when the assigned criterion was to win (F=6.801, P = 0.011).

In the dorsolateral prefrontal region

In the mRPS task, two-way ANOVA revealed a significant main effect of “group” in the following ch, but no significant interactions. The area of Δoxy-Hb in patients was significantly smaller than in the control group when the assigned criterion was to lose (left ch 11 (F=22.099, P <0.0001), right ch 12 (F=15.117, P = 0.0003)). In the control group, there were significant differences between the conditions (left ch 11: lose difference win (P = 0.0008), lose versus draw (P < 0.0001), right ch 12: lose versus draw (P < 0.0001). The maximum amplitude was significantly higher in the control group than in the patient group for all channels when the assigned criterion was to lose. In the control group, the maximum amplitude was significantly higher for left ch 11 when the assigned criterion was to lose compared with that to win (P = 0.0154) or draw (P = 0.0113). The latency time was significantly shorter in the control group than in the patient group when the assigned criterion was to lose (left ch 11 (F = 9.698,

P = 0.0028), right ch 12 (F = 5.898, *P* = 0.0182)). In the control group, the latency time was significantly shorter for left ch 11 when the assigned criterion was to lose compared with that to draw (*P* = 0.006).

In the parietal association area

In the mRPS task, two-way ANOVA revealed a significant main effect of “group” in the following ch, but no significant interactions. The area of Δoxy-Hb in patients was significantly smaller than in the control group when the assigned criterion was to lose (left ch 9 (F = 6.138, *P* = 0.0131), right ch 5 (F = 5.038, *P* = 0.0472)). In the control group, there were significant differences between the conditions (left ch 9: lose versus draw (*P* = 0.0045), right ch 5: lose versus draw (*P* = 0.0014)). The maximum amplitude was significantly higher in the control group than in the patient group for all channels when the assigned criterion was to lose (left ch 9 (F = 6.865, *P* = 0.0110), right ch 5 (F = 5.038, *P* = 0.0472)). In the control group, the maximum amplitude was significantly higher for left ch 9 when the assigned criterion was to lose compared with that to win (*P* = 0.0012) or draw (*P* = 0.001). In the same way, the maximum amplitude was significantly higher for right ch 5 when the assigned criterion was to lose compared with that to draw (*P* = 0.0014). The latency time was significantly shorter in the control group than in the patient group when the assigned criterion was to lose (left ch 9 (F = 6.865, *P* = 0.0110), right ch 5 (F = 7.842, *P* = 0.0068). In the control group, the latency time was significantly shorter for left ch 9 when the assigned criterion was to lose compared with that to win (*P* = 0.0012) or draw (*P* = 0.001). The latency time was significantly shorter for right ch 5 when the assigned criterion was to lose compared with that to win (*P* = 0.0028) or draw (*P* = 0.0024).

The integrated waveforms of each group in ROI and comparison among the tasks are shown in Figure 3(a) and 3(b). 3(a) shows integrated waveforms in the controls during each task, and 3(b) shows integrated waveforms in the patients. Figure3(c) shows Δoxy-Hb in the control group during the lose task, and it was significantly higher than in the other tasks, but no significant change was observed in the patient group.

Relation to social function

Correlation between Δoxy-Hb and PANSS scores or GAF scores

Under the win condition, Δoxy-Hb of left ch 11, left ch 19, and right ch 5 showed significant negative correlations with negative symptom scores of PANSS in patients (left ch 11 (r = -0.431, *p* = 0.0123), left ch 19 (r = -0.440, *P* = 0.0016), right ch 5 (r = -0.315, *P* = 0.047)). Under the draw condition, the Δoxy-Hb of left ch 9, left ch 11, left ch 19 and right ch 22 showed significant negative correlations with the negative symptom scores of PANSS in patients (left ch 9 (r = -0.316, *P* = 0.0123), left ch 11 (r = -0.431, *P* = 0.0004), left ch 19 (r = -0.440, *P* = 0.0048), right ch 22 (r = -0.342, *P* = 0.047)). Under the lose condition, the Δoxy-Hb of left ch 11, left ch 19ch and right ch 5 showed significant negative correlations with negative symptom scores of PANSS in patients (left ch 11 (r = -0.431, *P* = 0.0004), left ch 19 (r = -0.440, *P* = 0.0048), right ch 5 (r = -0.532, *P* = 0.0017)). However, there were no correlations with the positive scores or general psychopathology scores of PANSS. Furthermore, in the lose condition, a significant positive correlation was observed between Δoxy-Hb and GAF at left ch 11 (r = 0.502, *P* = 0.0043), left ch 19 (r = 0.427, *P* = 0.0014), and right ch 5 (r = 0.495, *P* = 0.004) (Figure 4).

Discussion

The Δoxy-Hb levels during the mRPS tasks employing the event-related design were compared between schizophrenia and healthy groups using multichannel NIRS. In the task, following the instructions, the subject responded orally to a visual hand-shaped stimulation presented on the screen. The subject had to memorize the hand command presented on the screen and carefully execute the task, suggesting the close involvement of WM. Furthermore, unlike conventional tasks [1,6-11], by only replying orally, we reduced the influence of the motor cortex related to the movement of the hand, and we were able to more accurately evaluate the subject's brain activity during the task.

In the healthy group, the blood flow level significantly increased during the task to lose compared with those during the conditions to win and draw in the ROI. Since the behavior to lose is different from the normal rule, ‘winning is everything’, the subject had to perform the task while controlling their desire to win, which required inhibition of the routine, the habitual cognitive tendency, i.e., inhibition of stereotypes. [1, 35] The observed increase in the PFC blood flow level during the condition to lose may have been associated with the control of impulses and the inhibitory function required to perform the task. In the DLPFC, which plays the most central role in WM, the Δoxy-Hb level significantly increased during the condition to lose compared with those to win and draw. [1, 6, 7] According to the multicomponent model of WM established by Baddeley [35] the DLPFC represents the action of the central executive function responsible for attention control in WM. This WM is limited by the capacity, and control through attention is essential for its efficient operation. Accordingly, dynamic attentional resource allocation is necessary as a system to

simultaneously adjust the retention and processing of information. No increase in blood flow was noted during the condition to draw, suggesting that the capacity resource distributed to the central executive function was low because the task to draw was interpreted as to copy the presented stimulation.

In the schizophrenia group, a significant decrease in blood flow was observed in the bilateral prefrontal cortical areas and dorsolateral prefrontal areas during the task to lose. Deficiency of the frontal lobe function was observed in a study reported by Okada et al. [37] in which schizophrenic patients and healthy subjects were initially evaluated using a mirror-drawing task and NIRS. The presence of frontal lobe dysfunction in schizophrenia was also reported by later studies using NIRS and various cognitive tasks, such as verbal fluency [19] Go/No Go [38] continuous performance tasks [39] and the trail-making test. [40] These also suggest the presence of impairments in inhibitory and attention-related executive functions in schizophrenia patients, reflected in the impairment of WM. The decrease in the Δoxy-Hb during the condition to lose in the schizophrenia group may have been due to the difference in the difficulty of the task. Similarly, the relationship between the WM load and frontal lobe activity was presented using an inverted-U curve by Van Snellenberg et al. [41], the curve shifted leftward in the schizophrenia group, suggesting that the brain activity peaked at a lower load level than that in the healthy group, i.e., the condition to lose may have been too difficult for the schizophrenia group. Actually, after completing the tasks, many patients stated their subjective impression that the condition to lose was difficult. Cerebral blood flow in the anterior-middle region of the parietal lobe, considered to correspond to the parietal association area, also most markedly increased during the condition to lose in the healthy group, but no significant difference was noted among the conditions. In the patient group, the increase in Δoxy-Hb during the task to lose

was smaller than that in the healthy group. Particularly, the change was smaller at right ch 5 than left ch 9, showing laterality. Baker et al. [42] evaluated the characteristics of functional associativity of 122 cerebral cortical regions in schizophrenia patients during rest with their eyes open using functional magnetic resonance imaging (fMRI), and observed that functional associativity was reduced in the frontal-parietal control network including the dorsolateral prefrontal, posterior medial prefrontal, temporoparietal cortices, and part of the posterior temporal cortex, suggesting that impairment of information processing, including the frontal-parietal network, in schizophrenia patients represents vulnerability of the neural basis, in addition to frontal lobe dysfunction. Based on this, we expected an increase in cerebral blood flow during the condition to lose compared with those to draw and win, but no significant difference was observed. A possible reason for this is as follows: Since the capacity resource is limited, the resource may have been more preferentially distributed to the central executive function and control of impulse and inhibitory functions located mainly in the anterior cingulate gyrus than to the prefrontal area-parietal network during the task to lose, because this is more difficult than the other tasks. Accordingly, it was assumed that although blood flow most markedly increased during the condition to lose in the anterior-middle region of the parietal lobe, the change was not significant.

In patients, the area, maximum amplitude, and latency obtained from measurements in ROI were significantly smaller than in the control group when the assigned criterion was to lose. Regarding the latency, a significant extension was noted during the condition to lose in ROI, excluding right ch 22, in the patient group compared with those in the healthy subject group. This may support the findings of a study on the event-related potential reported by

O'Donnell et al. [43] whereby the latency of the P300 component was extended in schizophrenia patients.

A significant positive correlation was noted between Δoxy-Hb and GAF scores at left ch 11, left ch 19, and right ch 5 during the mRPS task, and a significant inverse correlation was noted between Δoxy-Hb in all ROI and the negative syndrome scale of PANSS. Concerning the GAF scores, a previous study of VFT reported that the prefrontal lobe, especially the frontal pole area was positively correlated with the GAF. [18, 44] In this study, the correlation between GAF scores and the left front pole area (left ch 19) was considered to agree with the previous study. However, the correlation of the left DLPFC area (left ch11) and right parietal association area (right ch 5) was considered to require further study. Generally, it is reported that the DLPFC area is activated at the time of the WM task, and that it becomes more activate as the task load increases. [45] In neuropsychological research on schizophrenia, impairment with the DLPFC area and activity of WM has been reported, considered to be closely associated to WM and social function. [46] GAF scores are not only a mental assessment but also an index that comprehensively covers the social function, and we considered that it was not inconsistent with the correlation between GAF and left ch 11. In addition, Thakkar et al. reported a decrease of activity specificity in the right inferior parietal lobe of schizophrenic patients in an fMRI study using the imitation task, and this site is closely related to mirror neurons. [47] In other words, regarding right ch 5, it may be simply associated with activities of the visual association field, but it may be a result reflecting disorders of mirror neurons in patients with schizophrenia and related social function disorders. Concerning PANSS, although only negative scales of PANSS in the patient group showed a negative correlation with ROI, this result may have been influenced by the task and environment in which it was

demonstrated. In other words, it can be said that the brain activity sites correlated with the task differed in all of the previous studies revealing a

negative correlation between Δoxy-Hb and the negative scale of PANSS. [17, 33, 48] However, this study is consistent with the results of Fujiki et al. [17] whereby the schizophrenia group showed a negative correlation between the DLPFC region and negative symptom scale of PANSS. These results may reflect the negative correlation between the negative symptom scale of PANSS and execution function reported by Heydebrand et al. [49] Further studies are needed in order to clarify this point. Furthermore, it was recognized that no significant difference was observed between the working patient and healthy subject groups in Δoxy-Hb of ch 19. These findings suggest that it serves as a state marker reflecting the social function of schizophrenia patients, and the left frontal lobe (particularly left ch 19) reflects the central region responsible for social function. This is consistent with the positive correlation between the frontal pole region and GAF scores in schizophrenia patients observed using a verbal fluency task reported by Takizawa et al. [18] Therefore, this study design may support the prediction of a patient's response to treatment and the appropriateness of timing to reintegrate them into society. These results suggest that the extent of social function can be inferred by observing the relevant part of the NIRS measurement result, and as a condition evaluation of patients with psychiatric disorders, the significance of observing the degree of social life simultaneously with individual symptoms was considered. However, several problems still need to be addressed. Firstly, the difference in the performance should be clarified. Only the data of subjects with a success rate exceeding 80% were adopted, but the number of correct responses varied among individuals. Thus, it may be necessary to standardize the performance for accurate evaluation. Secondly, there is a problem with the NIRS device

itself. A characteristic of NIRS is its low spatial resolution, but individual MRI was not performed in this study. Thus, the validity of the anatomical region should be more closely investigated. In addition, artifacts are another problem. In fact, body movement such as nodding and shaking of the head causes artifacts. There is a possibility of changes in Hb due to contact failure of a fiber. The influence of skin blood flow is also known [50] and mechanisms to reduce these artifacts will be important in the future. The third problem is disease specificity. It is necessary to investigate whether the data were specific to schizophrenia, as well as their reproducibility and course observation. Finally, the influence of drugs should be considered because all patients were being treated with oral atypical antipsychotics. This confounding factor should be excluded by comparison with an untreated patient group, requiring further studies. Moreover, this study included patients whose performance level was higher than that of the healthy subjects, and local cerebral blood flow, mainly in the DLPFC, increased even under the condition to lose. These findings may support the hypothesis of hypo- and hyper-activation of the frontal lobe function in schizophrenia, which has been discussed. In a preceding study to compare healthy subjects with a schizophrenic patient group using a verbal fluency task, Watanabe and Kato [51] reported that patients showed performance comparable to that of a healthy subject group. Moreover, Shinba et al. [52] performed three types of frontal lobe activation task (random number generation task, ruler-catching task, and sequential finger-to-thumb task), with different findings among the tasks. There was a decrease in Δoxy-Hb in the random number generation and ruler-catching tasks, and there was no difference in the sequential finger-to-thumb task in patients. The difference in performance and the frontal lobe activation reaction can be considered to support not only the hyper/hypo frontality hypothesis, but also that the findings are task-dependent.

Furthermore, considering the laterality [38] and inefficiency of the brain function in schizophrenia, these findings may predict a failure of some kind at the nerve cell level, reflecting the complexity of frontal lobe function mechanisms in schizophrenia.

In summary, this is the first study comparing healthy subjects and schizophrenia patients during modified rock-paper-scissors, a frontal lobe cognitive task, using single-event-related NIRS. The oxygenated hemoglobin level decreased in the frontal lobe and anterior-middle region of the parietal lobe during the task in schizophrenia patients, and significant correlations were observed between these findings and GAF values and the negative symptom of PANSS. It was suggested that the modified rock-paper-scissors task is useful to evaluate the cognitive and social functions of schizophrenia patients using NIRS.

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Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

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Figure 1.

(a) The probe-holder worn by the participant.

(b) Location of channels, and region of interest.

Figure 2.

(a) Task design

The subjects said 「A・I・U・E・O…」 repeatedly for 12 seconds between presented black spots, and responded to the photo of the hand presented for 0.3 seconds as soon as possible. Each task was performed 20 times. This picture shows the lose condition of the mRPS task.

(b) An example of an integrated waveform. The measurement site is shown

in the figure.

Figure 3.

(a) Integrated waveform in the controls during each task. (b) Integrated waveform in the patients.

Figure 3.

(c) Δoxy-Hb in the control group during the lose task was significantly higher than in the other tasks, but no significant change was observed in the patient group.

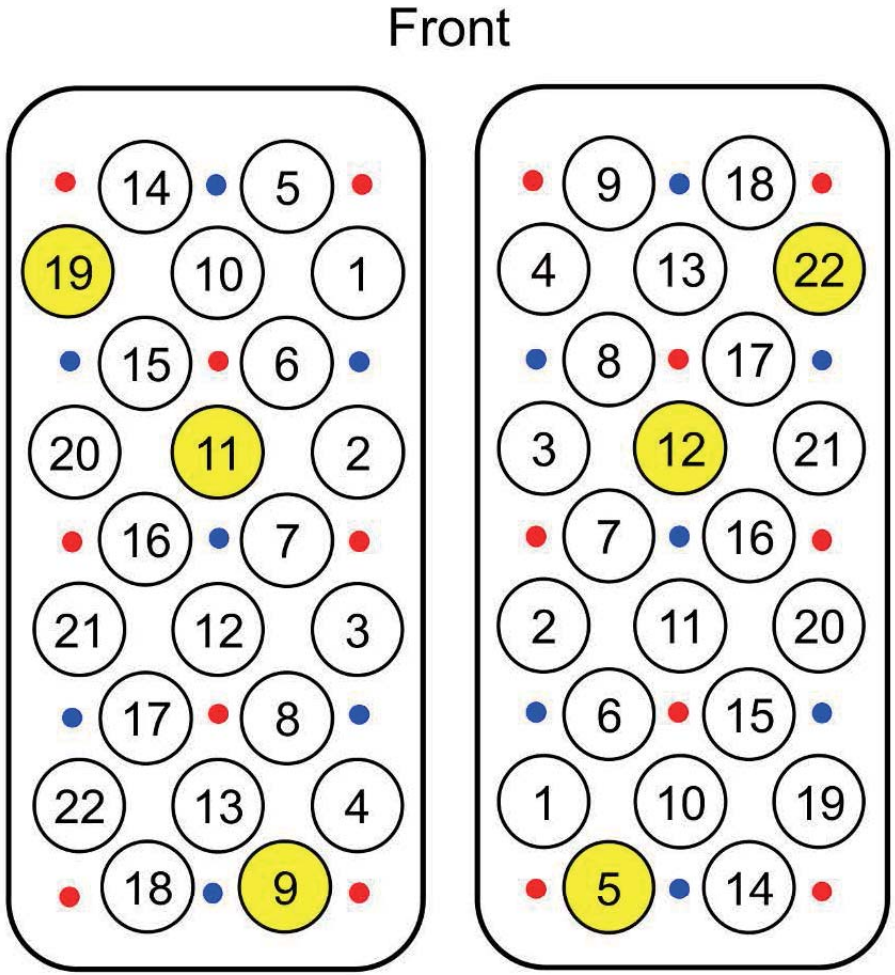
Note: Significance, ＊P < 0.05, ＊＊P < 0.01, ＊＊＊P < 0.001

Figure 4.

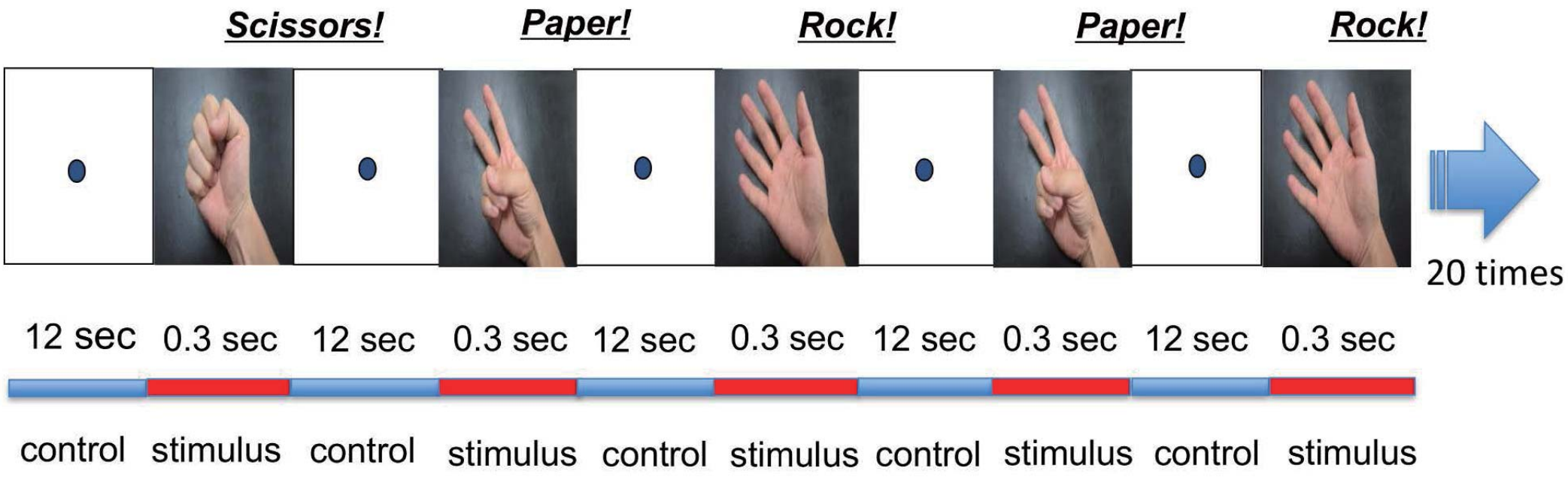
Relationship between Δoxy-Hb at left ch 19, left ch 11, right ch 5 and the negative symptom score, GAF in patients during the lose task.

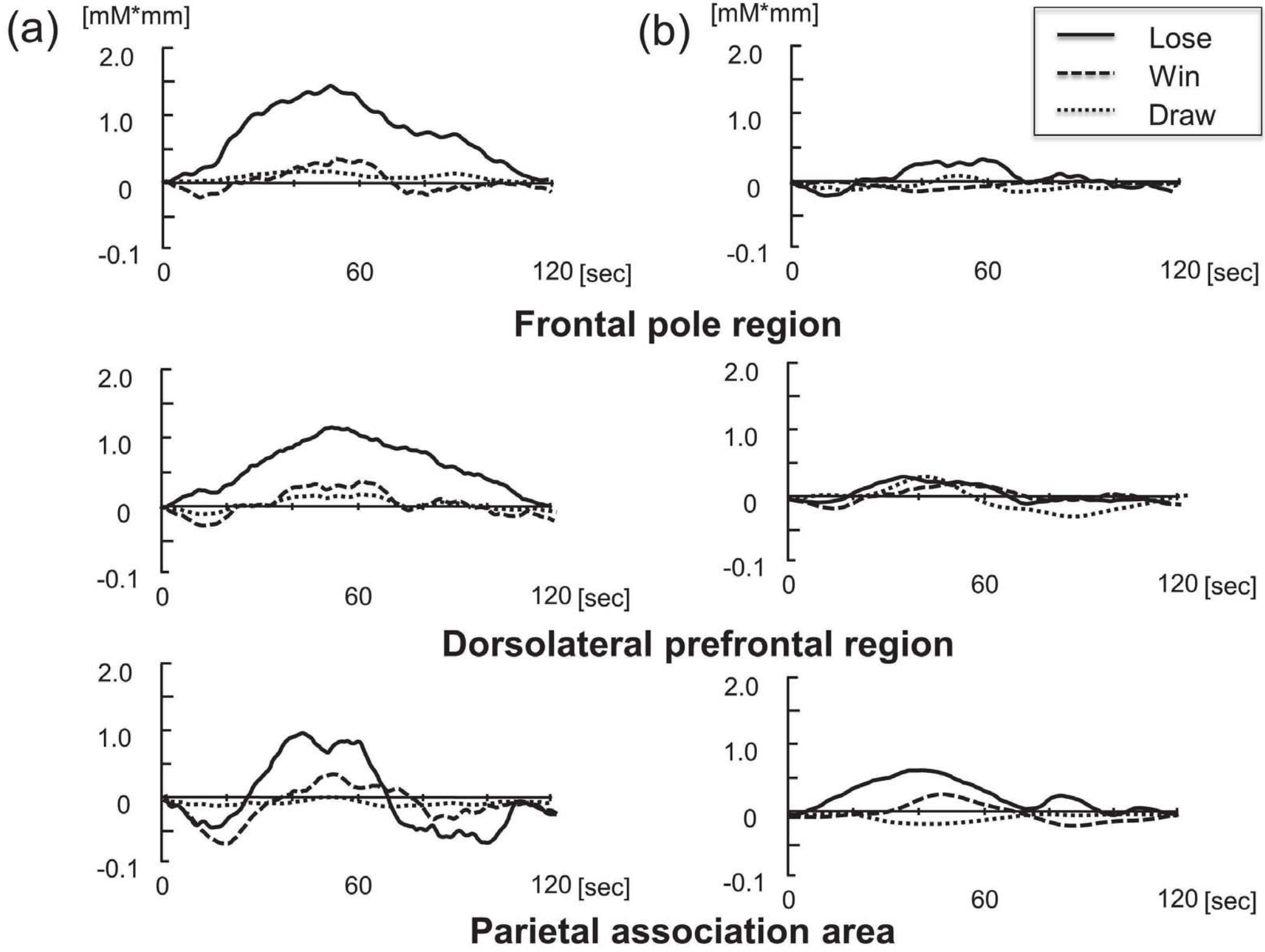
(a)

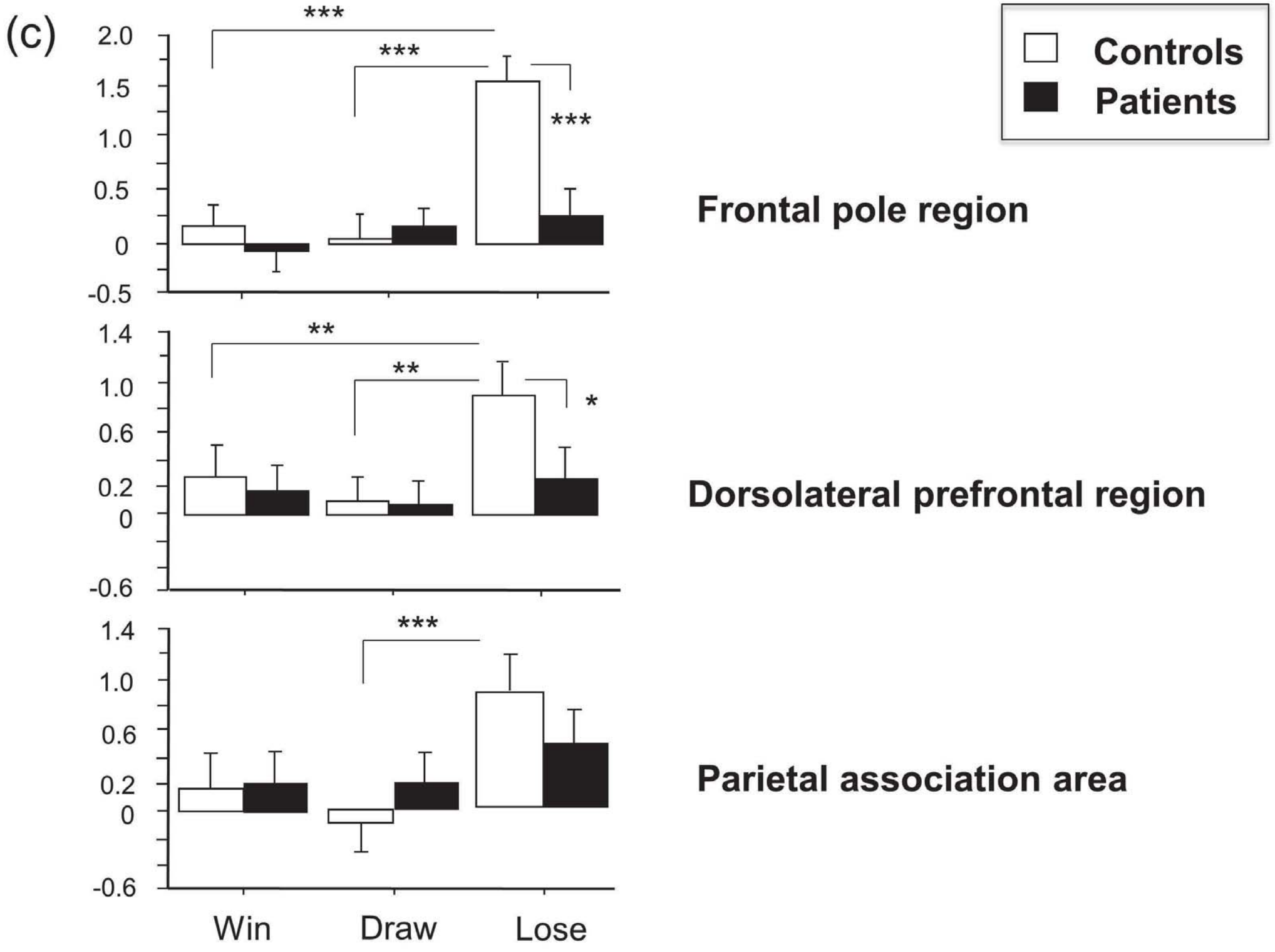
(b)

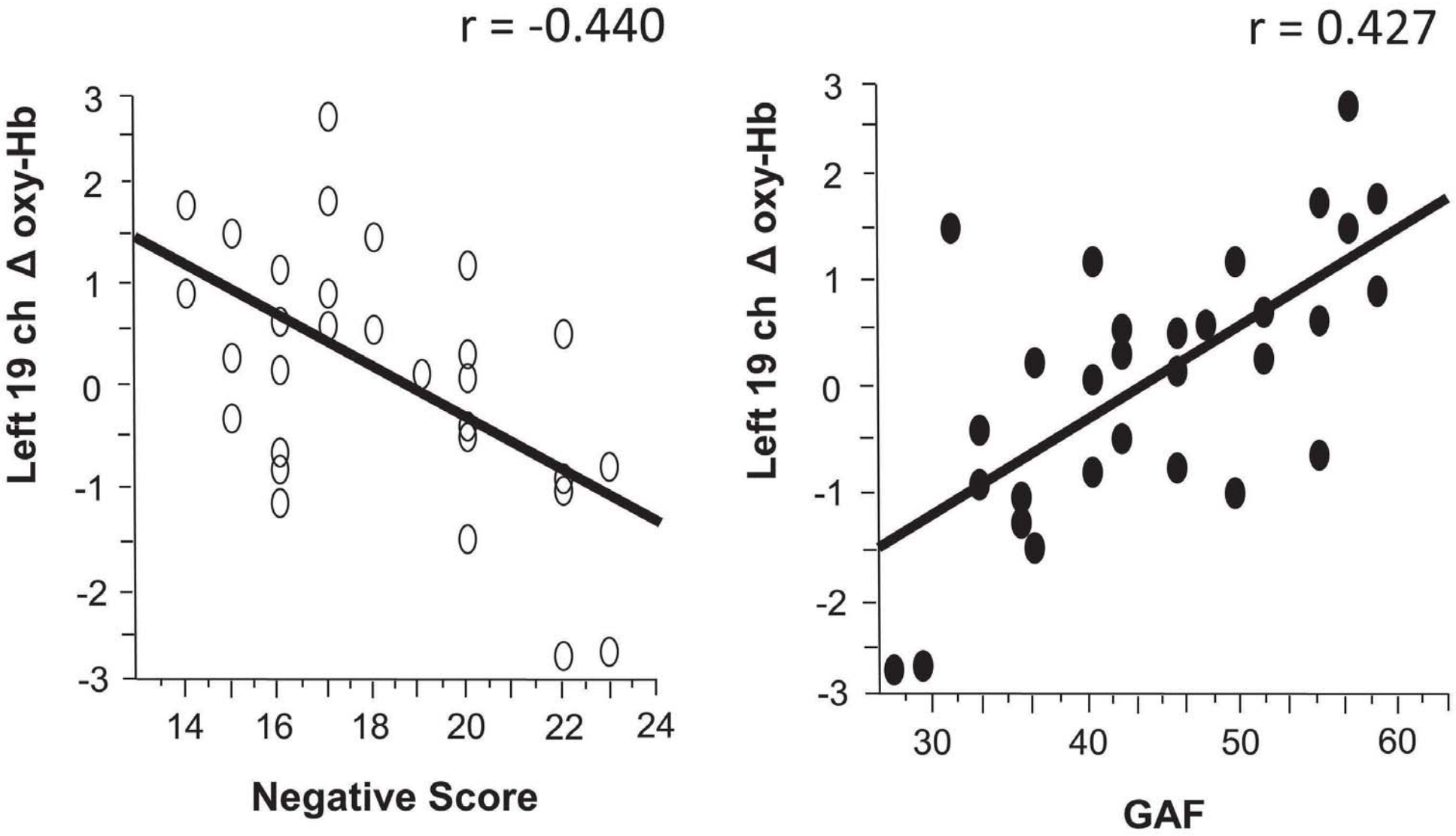


* Injector probes (●), detection probes (●), ROI (●)


Scissors!
Paper!
Rock!
Paper!
Rock!
20 times
12 sec
0.3 sec
12 sec
0.3 sec
12 sec
0.3 sec
12 sec
0.3 sec
12 sec
0.3 sec
control
stimulus
control
stimulus
control
stimulus
control
stimulus
control
stimulus


(a)
[mM*mm]
2.0
1.0
0
-0.1
0
60
120 [sec]
(b)
[mM*mm]
Lose
Win
Draw
Frontal pole region
Dorsolateral prefrontal region
Parietal association area


(c)
Controls
Patients
***
***
***
2.0
1.5
1.0
0.5
0
-0.5
Frontal pole region
**
**
*
1.4
1.0
0.6
0.2
0
-0.6
Dorsolateral prefrontal region
***
1.4
1.0
0.6
0.2
0
-0.6
Parietal association area
Win
Draw
Lose


r = -0.440
Left 19 ch Δ oxy-Hb
3
2
1
0
-1
-2
-3
14
16
18
20
22
24
Negative Score
r = 0.427
Left 19 ch Δ oxy-Hb
3
2
1
0
-1
-2
-3
30
40
50
60
GAF

	Patients (mean ± SD)	Controls (mean ± SD)	P-value
Age (years)	33.6±8.5	31.6±8.5	n.s.
Gender (F/M)	15/15	14/16	
Duration of illness (years)	7.4±4.0		
Education (years)	14.4±1.5	13.6±1.3	0.0024
Estimated IQ (JART)	93.0±7.1	101±8.5	0.0009
PANSS Positive	20.1±4.1		
Negative	18.1±2.8		
General psychopathology	45.6±5.6		
GAF	44.8±9.4		
Antipsychotics (Risperidone equivalents) (mg/day)	4.4±1.3		

Notes: Data are presented as means ± standard deviation. $P < 0.05$, comparing patients with controls.

Abbreviations: F, female; GAF, Global Assessment of Functioning scale; IQ, intelligence Quotient; JART, Japanese version of the National Adult Reading Test; M, Male; PANSS, Positive and Negative Syndrome Scale.