学位論文の関連論文の研究背景及び要旨

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〔題名〕

Blunted brain activation in patients with schizophrenia in response to emotional cognitive inhibition: A functional near-infrared spectroscopy study

(統合失調症患者における情動認知抑制課題中の脳機能低下：多チャンネル機能的近赤外線スペクトロスコピー研究)

〔研究の背景及び要旨〕

統合失調症（Schizophrenia; SZ）患者は、情動顔の処理や認知抑制の障害を示し、社会機能の低下とも関連している。SZの機能的MRI研究において、情動顔の情動を判断させる課題中に上前頭回、海馬傍回、扁桃体が低活動を示し、また、認知抑制課題中に前頭前皮質、前部帯状回が低活動を示すという報告がそれぞれされている。しかしながら、日常では相手の表情をよんで、自分の行動を制御・抑制を行うという両者が相互に作用しあう関係にあるが、こうした複雑な相互作用に関してSZの脳機能に与える影響についてはいまだ明らかにされていない。近赤外線スペクトロスコピー（near-infrared spectroscopy; NIRS）は、近赤外光を用いて脳表の脳活動を測定する装置で、非侵襲的かつ自然な座位での測定も可能であるため、精神疾患患者への使用に適している。本研究では、NIRSを用いて、情動顔処理と認知抑制の相互作用を評価する情動顔go/no-go課題中の脳活動を測定し、課題成績と共にSZ患者と健常者の比較検討を行った。

対象は、山口大学医学部附属病院精神神経科及び片倉病院に通院もしくは入院中のSZ患者25名（平均年齢41.3±8.1歳、推定IQ99.4±10.8）、年齢と推定IQが統計的に一致した健常者28名。この研究は、山口大学医学部附属病院Institutional Review Board及び片倉病院倫理委員会の承認を得ており、全ての患者および健常者に、文書および口頭で研究の趣旨を説明し、文書による同意を得た。SZの診断は、米国精神医学会発行の精神疾患の分類と診断の手引き（DSM-IV）に基づく精神疾患簡易構造化面接法（M.I.N.I.）を用いて行った。SZ患者は全て抗精神病薬を服用しており、服用していた抗精神病薬のクロルプロマジン換算量を求め、罹病期間、入院回数も調べた。Positive and Negative Syndrome Scale (PANSS)を用いて精神症状（陽性、陰性、解体、興奮、抑うつの5項目）の評価を行い、Global Assessment of Functioning (GAF)を用いて社会機能の評価を行った。健常者もM.I.N.I.を行い、精神疾患に罹患していないことを確認した。情動顔go/no-go課題は、情動顔刺激を用いた情動課題と情動を伴わない中性顔を用いた非情動課題で構成し、情動顔には陰性の情動（恐怖、怒り）を用いた。被験者には、指定されたgo刺激が、スクリーン上に呈示された場合のみ手元の押しボタンを押すよう教示し、偽陽性率（押してはいけない刺激で誤って押した割合）、偽陰性率（押さなくてはならない刺激で誤って押さなかった割合）、正答時の反応時間を測定した。NIRSは、日立メディコ社製ETG-4000を用い、脳波の国際10 - 20法に従ってプローブを頭部に装着し、両側の前頭前皮質と側頭皮質表面の全31チャンネルにおける、情動顔go/no-go課題中の酸素化ヘモグロビン濃度（[oxy-Hb]）変化を測

定した。統計解析は、課題成績において、課題内容を被験者内要因に、診断を被験者間要因として二元配置分散分析を行い課題内容と診断との交互作用を評価し、有意差を認めた課題成績と患者背景及び精神症状との関連を、ピアソン相関係数を用いて調べた。NIRSデータは、スチューデントt テストを用いて各チャンネルの平均[oxy-Hb]変化を群内及び群間で比較し、false discovery error (FDR)補正を行った。群間比較にて有意差を認めたチャンネルの平均[oxy-Hb]変化と患者背景及び精神症状との関連を、ピアソン相関係数を用いて調べた。

結果、課題成績では、偽陽性率、偽陰性率、反応時間について課題内容の主効果が認められ、偽陽性率と反応時間について課題内容と診断との交互作用が認められた。SZ患者において、情動課題中の偽陽性率は、PANSSの陰性、解体、興奮症状と正の相関を示し、GAFと負の相関を示した。非情動課題では、偽陰性率とPANSSの興奮症状とが正の相関を示し、反応時間とGAFが負の相関を示した。いずれの課題成績も抗精神病薬服用量との相関を認めなかった。NIRSデータは、健常者では非情動課題に比べ、情動課題において有意に左上前頭、左下前頭、両側眼窩前頭領域の[oxy-Hb]の増大がみられたが、SZ患者では両課題で有意差のある脳部位は認められなかった。また、健常者はSZ患者と比べて情動課題中の左上前頭、両側眼窩前頭、左中側頭領域の[oxy-Hb]が有意に増大していた。SZ患者では、情動課題中の左眼窩前頭領域の[oxy-Hb]は入院回数と負の相関を示したが、補正後は有意な相関を認めなかった。また、SZ患者では、情動課題中の左上前頭、両側眼窩前頭、左中側頭領域の[oxy-Hb]と、抗精神病薬服用量を含むその他の患者背景、精神症状との有意な相関は認めなかった。

今回認められたSZ患者における情動顔判別および認知抑制の障害は、行動学的特徴、脳画像所見ともに、類似した先行研究の結果を支持していた。SZ患者において、情動課題中の機能低下がみられた脳部位は、情動認知に加え、情動制御や反応抑制に関与していることが報告されており、SZ患者では前頭前皮質及び中側頭皮質の機能異常が、情動顔判別および認知抑制障害の病態生理に関与している可能性が示唆された。SZ患者の情動顔処理や認知抑制時の機能異常が報告されている扁桃体や前部帯状回などの深部領域は、NIRSでは測定困難なため、結果の解釈には注意が必要であるが、今回得られた結果がSZ患者における社会的相互作用障害の病態理解に寄与できるかもしれない。

Blunted brain activation in patients with schizophrenia in response to emotional cognitive inhibition: A functional near-infrared spectroscopy study

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Abstract

Introduction: Patients with schizophrenia (SZ) have deficits of facial emotion processing and cognitive inhibition, but the brain pathophysiology underlying these deficits and their interaction are not clearly understood. We tested brain activity during an emotional face go/no-go task that requires rapid executive control affected by emotional stimuli in patients with SZ using functional near-infrared spectroscopy (fNIRS).

Methods: Twenty-five patients with SZ and 28 healthy control subjects were studied. We evaluated behavioral performance and used fNIRS to measure oxygenated hemoglobin concentration changes in fronto-temporal areas during the emotional go/no-go task with emotional and non-emotional blocks.

Results: Patients with SZ made more errors and had longer reaction times in both test blocks compared with healthy subjects. Significantly greater activation in the inferior, superior, middle, and orbital frontal regions were observed in healthy subjects during the emotional go/no-go block compared to the non-emotional go/no-go block, but this difference was not observed in patients with SZ. Relative to healthy subjects, patients with SZ showed less activation in the superior and orbital frontal and middle temporal regions during the emotional go/no-go block.

Discussion: Our results suggest that fronto-temporal dysfunction in patients with SZ is

due to an interaction between abnormal processing of emotional facial expressions with negative valence and cognitive inhibition, especially during the rapid selection of rule-based associations that override automatic emotional response tendencies. They indicate that fronto-temporal dysfunction is involved in the pathophysiology of emotional-cognitive deficits in patients with SZ.

Keywords

Emotion; Near-infrared spectroscopy; Face expression; Cognitive inhibition; Schizophrenia

1 Introduction

Patients with schizophrenia (SZ) have been shown to have abnormalities of face perception and emotional face processing in behavioral and neuroimaging studies (Marwick and Hall, 2008; Tremeau, 2006, for review). Emotional processing deficits involving social cognition are associated with poor functional outcomes (Hooker and Park, 2002) and negative symptoms (Chan et al., 2010) in patients with SZ. Behavioral studies suggest that patients with SZ tend to misinterpret neutral faces as negative emotional faces (Cohen et al., 2010; Habel et al., 2010; Kohler et al., 2003) and are impaired in processing emotional aspects of facial expressions affected for specificity (correct rejection of a non-target emotion) but not sensitivity (correct identification of a target emotion) (Habel et al., 2010; Schneider et al., 2006; Seiferth et al., 2009).

Several brain regions are thought to be involved in face recognition: the inferior occipital gyrus for early perception of facial features; the superior temporal sulcus for changeable aspects of face-perception; the lateral fusiform gyrus for invariant aspects of face-perception; the amygdala, insula, and limbic system for assessment of emotion; the anterior temporal cortex for personal identity, name, and biographical information (Haxby et al., 2000); and the prefrontal and orbitofrontal cortices for appraising the emotional significance of stimuli and guiding social decisions and behavior (Adolphs et al., 2000;

Damasio, 2005). A meta-analysis of functional neuroimaging studies revealed that patients with SZ showed remarkable under-recruitment of the superior frontal gyrus, parahippocampus, amygdala, and middle occipital gyrus in response to emotional faces (Li et al., 2010) and increased activity in the dorsolateral prefrontal cortex, middle orbital gyrus (Habel et al., 2010), amygdala (Hall et al., 2008; Holt et al., 2006) and parahippocampus (Surguladze et al., 2006) in response to neutral faces. Such differences might be a consequence of aberrant attribution of emotional meaning to neutral stimuli (Habel et al., 2010).

Patients with SZ are also less able to control cognitive inhibition. In functional magnetic resonance imaging (fMRI) studies during cognitive inhibition tasks (e.g., go/no-go) patients with SZ showed hypoactivation of the dorsolateral and ventrolateral prefrontal cortices and dorsal anterior cingulate cortex and hyperactivation of the superior parietal lobule compared to healthy subjects (Arce et al., 2006; Kaladjian et al., 2007; Kiehl et al., 2000; Laurens et al., 2003). In a functional near-infrared spectroscopy (fNIRS) study, patients with SZ had greater activation of post-central region compared to healthy subjects during a go/no-go task (Nishimura et al., 2011).

The interaction between emotional processing and cognitive function was impaired in patients with SZ, which contributed to poor social functioning (Park et al., 2008). Prior

fMRI studies of emotional-cognitive interaction in patients with SZ employed a Stroop task with emotional pictures or go/no-go task with emotional words and suggested that SZ was characterized by inefficient top-down control and an association of dorsal and ventral frontal brain regions (Park et al., 2008; Vercammen et al., 2012). However, to our knowledge, no neuroimaging study has assessed the interaction between emotional face recognition and cognitive inhibition in patients with SZ. The interaction is useful for evaluating emotional control accompanied by social-cognitive interactions that require the rapid selection of rule-based associations that override automatic emotional response tendencies (Volman, 2011). The present study used an emotional go/no-go task with emotional faces combined with cognitive inhibition. This task was also expected to elucidate the subjects' ability to correctly reject irrelevant emotional information that could alter target emotion processing, which has been reported to be affected in patients with SZ (Habel et al., 2010; Schneider et al., 2006; Seiferth et al., 2009).

Near-infrared spectroscopy (NIRS) is a technology that assesses brain function; it measures real-time hemodynamics over the surface of the prefrontal cortex with infrared spectrum light. The signals measured by functional NIRS (fNIRS) correlate strongly with those measured by fMRI (Huppert et al., 2006; Toronov et al., 2001). The fNIRS instrument is small, convenient, noninvasive, is relatively insensitive to motion artifacts,

and can be used in a natural seated position without any noise or pain. These advantages make it suitable to assess brain function in adults with psychiatric disorders such as schizophrenia (Takei, et al., 2013; Takizawa, et al., 2008) and mood disorders (Matsubara, et al., 2014; Matsuo, et al., 2007). In the content of social cognition, Takei et al. (2013) investigated brain activation during a face-to-face conversation task in patients with SZ and found decreased activation in the temporal lobes and the right inferior frontal gyrus. However, to our knowledge, there are no fNIRS studies that have investigated the interaction between emotional face recognition and cognitive inhibition in patients with SZ.

Here, we examined brain activation in patients with SZ during an emotional go/no-go task using multi-channel fNIRS. Based on the findings of previous neuroimaging studies, we hypothesized that patients with SZ would show inferior behavioral performance and blunted activation of fronto-temporal regions during the task.

2 Materials and Methods

2.1 Subjects

A total of 53 individuals matched for age, sex, handedness, and premorbid intelligence

quotient (IQ) participated in this study, including 25 patients with SZ diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) and 28 healthy subjects (Table 1). The patients included outpatients and inpatients being treated at Yamaguchi University Hospital and Katakura Hospital. Healthy subjects were recruited by advertisements and word-of-mouth in the community. This study was approved by the Institutional Review Board of Yamaguchi University Hospital and the ethics committee of Katakura Hospital. After the study was fully described to each subject, we obtained written informed consent from all participants. Patients were diagnosed using a clinical interview, scores on the Mini-International Neuropsychiatric Interview (M.I.N.I., Japanese version 5.0.0) (Otsubo et al., 2005), and conferences among psychiatrists. All patients were medicated with first-generation antipsychotics (n = 1), second-generation antipsychotics (n = 13), or both (n = 11). Doses of medication prescribed for the patients at the time of study participation were converted into chlorpromazine-equivalents (CPZ-eq). The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) was used to assess psychiatric symptoms. We used a five-factor model of PANSS comprising 20 items categorized into Positive, Negative, Disorganized/Concrete, Excited, and Depressed factors (Wallwork et al., 2012). The duration of illness and the duration of untreated psychosis (DUP) were also assessed.

Any participant who had a neurological illness; a history of traumatic brain injury with loss of consciousness; alcohol or drug abuse; or any physical illness, such as hepatitis, brain tumor, or epilepsy was excluded from the study. Healthy subjects were screened with the M.I.N.I. We excluded healthy participants with first- or second-degree relative(s) with a history of psychiatric disorders. Premorbid IQs were estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). The Global Assessment of Functioning scale (American Psychiatric Association, 2000) was used to assess social functioning.

2.2 Emotional go/no-go task

In fMRI studies using an emotional go/no-go task to assess cognitive-emotional interference in patients with another psychiatric condition such as bipolar disorder (Hare et al., 2008; Todd et al., 2012; Wessa et al., 2007), go trials (target stimuli) occurred from 50–70% of the trials. The stimuli were fearful, angry, and happy faces that were presented for 0.5 s with a 1- to 2-s interstimulus interval. Based on these studies and our pilot trials, we set the presentation of face stimuli for 1-s with a 1-s interstimulus interval considering the task difficulty for patients with SZ. We also adopted faces with negative emotions of fear and angry as emotional stimuli because those showed greater deficit of the face processing for negative emotions compared to that for positive emotion (Kohler

2003AJP). The emotional go/no-go task consisted of go and no-go trials in emotional, non-emotional, and control blocks (Figure 1). The entire task took 404 s and consisted of five blocks, including one emotional block with emotional faces, one non-emotional block with neutral faces, and three control blocks with geometrical figures (Figure 1). For go trials, participants responded by pressing a button on a keypad with the index finger of their preferred hand as fast as possible when a given target stimulus (e.g., angry face) appeared. Participants were instructed to withhold pressing a button on no-go trials (e.g., fearful face). Go and no-go trials each comprised 50% of the task. The emotional and non-emotional blocks were placed between the control blocks. In the emotional block, face pictures of two negative emotional expressions (anger and fear) were used as stimuli, and one of them was the target emotion. The emotional block consisted of two types of emotional tasks using negative emotional faces: go-anger and no-go-fear or go-fear and no-go-anger. In the non-emotional block, participants were required to identify the sex of the neutral face pictures, and these also consisted of two types of non-emotional tasks (go-male and no-go-female or go-female and no-go-male). The presentation of stimuli, choice of target stimuli, and emotional and non-emotional go/no-go task order were administered in a counterbalanced order across subjects. We recorded participants' accuracy rates and reaction times. As there were 32 trials in each activation block, 76 s

were required for completion (Figure 1). The Japanese and Caucasian Facial Expressions of Emotion and Neutral Faces (Matsumoto and Ekman, 1988) were used as cue and response choice stimuli in the emotional and non-emotional blocks. The control block was a sensorimotor go/no-go task with the same instructions in which subjects responded to geometric shapes (square or circle).

2.3 fNIRS measurement

We used a continuous-wave NIRS system (ETG-4000, Hitachi Medical Co., Japan) to collect fNIRS data. Relative changes in the concentrations of oxygenated and deoxygenated hemoglobin ([oxy-Hb] and [deoxy-Hb], respectively) were monitored using a 52-channel NIRS machine with 16 detectors and 17 emitters (Matsubara et al., 2014). Relative [oxy-Hb] changes were estimated according to the Beer–Lambert law using the difference in absorption between the two wavelengths of near-infrared light (695 and 830 nm). The distance between pairs of emitter and detector probes was 3 cm, which measures approximately 2–3 cm beneath the scalp (Okada and Delpy, 2003; Toronov et al., 2001). The measured area between an emitter and detector probe was defined as a channel. The lowest probes were positioned along the Fp1–Fp2 line according to the international 10/20 system for electroencephalography. Probes were placed over the frontal and temporal areas. The time resolution was set at 0.1 s.

The data were analyzed using the integral mode, in which the pre-task baseline during the control block was determined as the mean [oxy-Hb] during the 10 s just prior to the task period, the post-task baseline during the control block was determined as the mean [oxy-Hb] of the last 10 s in the post-task period, and the data between two baselines was linearly fitted. Similar to recent fNIRS studies (Takei et al., 2013; Takizawa et al., 2008) we employed the inferior 31 channels of 52 channels for statistical analysis. Acquired [oxy-Hb] changes were smoothed with a moving average method, and the duration of the moving average was set at 5 s. The channel records with low signal-to-noise ratios or motion artifacts were excluded by an expert on fNIRS (KM) who was unaware of the subject's diagnosis and task performance. The correspondence between NIRS channels and brain regions was confirmed (Okamoto et al., 2004). We anatomically identified the location of channels using a virtual registration method with automated anatomical labeling (Tzourio-Mazoyer et al., 2002) that enables NIRS channel positions to be registered on the standard brain space (Tsuzuki et al., 2007).

2.4 Statistical analysis

2.4.1 Behavioral data

Chi-square test for sex and Student's t-tests for age and education were used to compare demographic characteristics between patients with SZ and healthy subjects. Task

performance was assessed by the false alarm error rate (number of incorrect response/all correct withholding to no-go trials), omission error rate (number of incorrect no response/all correct response to go trials), and reaction time (for correct hits) for each block condition. We performed two-way analysis of variance (ANOVA) with task as a within-factor and diagnosis as a between-factor at each behavioral parameter. In patients with SZ, correlation analysis was carried out to compare behavioral performance and clinical variables (i.e., duration of illness, the number of hospitalization, DUP, GAF, PANSS subscores, and CPZ-eq) between the two groups using Bonferroni-corrected Pearson correlation coefficients. We used SPSS software for Windows, version 16.0 (SPSS, Inc., Chicago, IL) for statistical analyses. Differences were considered significant at 0.05.

2.4.2 fNIRS

For within-group comparison, we tested differences of mean [oxy-Hb] and [deoxy-Hb] changes at each channel by performing Student's t-tests for each channel between the emotional and non-emotional blocks in patients with SZ and healthy subjects, respectively. We carried out a between-group comparison to examine the difference of mean [oxy-Hb] and [deoxy-Hb] changes for each channel by Student's t-tests between the patients with SZ and healthy subjects in the emotional and non-emotional blocks, respectively. We also

statistically analyzed differences in mean [oxy-Hb] and [deoxy-Hb] changes at different channels using two-way ANOVA with the task and diagnosis as the within- and between-factors, respectively. Statistical significance was set at $p < 0.05$, and false discovery rate (FDR) correction for the multiple comparisons among 31 channels was performed as described previously for fNIRS studies (Singh and Dan, 2006). Among the patients with SZ, a Bonferroni-corrected Pearson correlation coefficient was calculated to investigate the relationships between different clinical variables and the mean [oxy-Hb] and [deoxy-Hb] changes at the channels determined to be significant in the between-group comparison.

3 Results

3.1 Demographics and task performance

There were no significant differences in demographic variables between patients with SZ and healthy subjects except in years of education (Table 1). There was a significant interaction between task and diagnosis for both reaction time ($F = 8.56$, $p = 0.005$) and false alarm error rate ($F = 8.33$, $p = 0.006$) and a significant effect of task on reaction time ($F = 107.7$, $p < 0.001$), omission error rate ($F = 31.8$, $p < 0.001$) and false alarm error rate ($F = 16.9$, $p < 0.001$) (Table 2).

In patients with SZ, a higher false alarm error rate in the emotional go/no-go block was significantly positively correlated with the negative ($r = 0.55$, $p = 0.02$), disorganized ($r = 0.68$, $p < 0.01$), and excitement factors of the PANSS ($r = 0.73$, $p < 0.01$) and negatively correlated with GAF scores ($r = -0.55$, $p = 0.02$). Reaction time was positively correlated with illness duration ($r = 0.65$, $p < 0.01$). In the non-emotional go/no-go block, a higher omission error rate was significantly positively correlated with the PANSS excitement factor ($r = 0.62$, $p < 0.01$), and the mean reaction time was positively correlated with negative PANSS factors ($r = 0.60$, $p < 0.01$) and negatively correlated with GAF scores ($r = -0.52$, $p = 0.04$). None of the behavioral parameters was significantly correlated with CPZ-eq.

3.2 fNIRS

In the within-group comparison, healthy subjects showed significantly greater [oxy-Hb] increases in seven channels (#29, #37, #38, #39, #46, #48, and #49) during the emotional go/no-go block compared to the non-emotional go/no-go block, corresponding to the left inferior, superior, and left and right orbital frontal regions (Figure 2A and 2C, Table 3). Healthy subjects also showed a significant [deoxy-Hb] decrease in channel #47, estimated to be the right orbitofrontal region. Patients with SZ showed similar time courses of mean [oxyHb] changes during the emotional and non-emotional go/no-go blocks (Figure 2B),

and we did not observe significant differences in [oxy-Hb] or [deoxy-Hb] changes between the two blocks. No other significantly different [oxy-Hb] or [deoxy-Hb] was observed at any channel between the emotional and non-emotional go/no-go blocks in healthy subjects or patients with SZ.

In the between-group comparison, relative to healthy subjects, patients with SZ showed attenuated [oxy-Hb] increases in four channels (#37, #38, #42, #47, and #48) during the emotional go/no-go block; they corresponded to the left superior frontal, left middle temporal, and left and right orbitofrontal regions, respectively (Figure 3 and Table 4). No channel showed a significantly greater [oxy-Hb] increase in patients with SZ compared to healthy subjects. Patients with SZ showed significant [deoxy-Hb] increases at #39 compared to healthy subjects, which was estimated to be the left middle frontal region. During the non-emotional go/no-go block, there was no significant difference of [oxy-Hb] or [deoxy-Hb] between patients with SZ and healthy subjects.

Two-way ANOVA revealed that [oxy-Hb] change showed a significant interaction between the task and diagnosis in channel #25 ($F = 4.70$, $p = 0.03$), #28 ($F = 4.05$, $p = 0.049$), #37 ($F = 7.73$, $p = 0.008$), #38 ($F = 12.6$, $p = 0.0008$; $F = 5.41$), #47 ($F = 4.88$, $p = 0.03$), #48 ($F = 9.61$, $p = 0.003$), and #49 ($F = 5.10$, $p = 0.03$) and a significant effect of task in # 36 ($F = 4.85$, $p = 0.03$), #37 ($F = 5.50$, $p = 0.02$), #38 ($F = 5.41$, $p = 0.02$),

#45 (F = 6.63, p = 0.01), #46 (F = 6.42, p = 0.02), #49 (F = 5.85, p = 0.02), and #50 (F = 5.49, p = 0.02). The significant interaction of # 38 and #48, corresponding to the left superior frontal and orbitofrontal regions, survived after FDR correction.

The mean [oxy-Hb] in channel #48 with significance in the between-group comparison was significantly inversely correlated with the number of hospitalizations (r = -0.43, p = 0.03) in patients with SZ, but it was not significant after multiple comparison correction. No other significantly different [oxy-Hb] or [deoxy-Hb] at any channel was correlated with clinical variables in the between-group comparison.

4 Discussion

4.1 Primary results of the study

The results of the current study demonstrate that patients with SZ showed similar fronto-temporal region activations for the non-emotional and emotional go/no-go tasks, whereas healthy subjects exhibited greater activation in the superior, inferior, and orbital frontal and middle temporal regions during the emotional task compared to the non-emotional go/no-go task. Compared to healthy subjects, patients with SZ showed blunted activations during the emotional go/no-go task in the superior and orbital frontal and temporal regions, with more pronounced decreases in the frontal regions. Reduced orbitofrontal region

activation tended to be associated with more frequent hospitalizations in patients with SZ. Poorer behavioral performance was associated with more severe SZ. These findings suggest that dysfunction of fronto-temporal regions, particularly the superior and orbitofrontal regions, is associated with the interaction between abnormal processing of emotional facial expressions with negative valence and cognitive inhibition in patients with SZ, especially during the rapid selection of rule-based associations that override automatic emotional response tendencies. It is likely that such deficits are involved in the pathophysiology underlying emotional-cognitive complex deficits in patients with SZ, including social situations.

4.2 Abnormal fronto-temporal function in response to emotional-cognitive stimuli in SZ

The frontopolar region including a part of the superior frontal region was activated by emotional tasks in normal volunteers, such as rating one's emotions in response to pictures of varying valence in contrast to the more posterior region activated by cognitive tasks such as those designed to engage action monitoring and attention (Amodio and Frith, 2006). The orbital frontal regions were also activated during the withholding of a response (Horn et al., 2003), during emotional regulation processes (Beauregard et al., 2004), and under the affect-incongruent responses (i.e., responses to emotional faces that conflict

with the automatic approach-avoidance reaction evoked by the emotional face, such as approach angry faces and avoid happy faces) (Roelofs et al. 2009).

The superior temporal sulcus (STS) separates the superior temporal gyrus from the middle temporal gyrus, and the functional territory for the posterior STS is thought to inferiorly extend to at least the posterior middle temporal gyrus (Wible et al., 2012). STS activity increases in response to incongruence between actions and intentions established by a previous emotional expression (Wyk et al., 2009). STS activity appears to be more enhanced during selective attention to facial emotion than during attention to the face per se (Narumoto et al., 2001).

The blunted activation of the superior frontal, orbitofrontal, and middle temporal regions during emotional face tasks was reported in previous studies of patients with SZ (Habel et al., 2010; Leitman et al., 2011; Li et al., 2010; Li et al., 2012). A meta-analysis of brain function during facial emotion perception tasks with any emotions demonstrates that patients with SZ, relative to control subjects, showed lower activation of superior frontal gyrus, parahippocampal gyrus/amygdala and middle occipital gyrus (Li et al., 2010). In other fMRI studies, patients with SZ, compared to healthy subjects, showed blunted activation of right superior frontal gyrus during a facial valence discrimination task using sad faces (Li et al., 2012), lower activation of inferior frontal gyrus adjacent to

orbitofrontal gyrus, anterior cingulate and cuneus during an emotional discrimination task using fear faces and inferior frontal gyrus, middle temporal gyrus, superior temporal gyrus and other areas during the task using angry faces (Habel, et al., 2010) and blunted activation of orbitofrontal gyrus during a facial affect detection task using fear and anger faces as well as happy and sad faces (Leitman et al., 2011). The results of current study that patients with SZ showed blunted activation of superior frontal and orbitofrontal gyrus and middle temporal gyrus in response to emotional facial stimuli further supports previous findings.

With regard to brain function underlying the interaction between emotional faces and cognitive control, an fMRI study in normal volunteers using an emotional go/no-go task with aversive distractor images revealed that the posterior middle temporal gyrus and angular gyrus exhibited larger activation for aversive distractor trials compared to neutral distractor trials, suggesting involvement of the middle temporal gyrus in impulse control evoked by emotional situations (Brown et al., 2012). An fMRI study of patients with SZ demonstrated that during an emotional go/no-go task using emotional words (i.e. positive, negative, and neutral words), the patients showed lower activation of the superior/middle frontal gyri and other areas in response to negative words. No significantly different activations were observed in response to positive words in contrast to neutral words,

compared to healthy subjects (Vercammen, et al., 2012). The investigators also found that patients with SZ showed no differential activation during the negative emotional block relative to the neutral block and more activation of right middle frontal gyrus during the positive emotional block relative to the neutral block. They therefore suggested that SZ is associated with abnormal modulation of the neural response in dorsal regions during negative emotional and inhibition processes and more anterior regions during positive emotional and inhibition. These findings are agreement with the results of the present despite the use of different study designs, task paradigms, and imaging devices.

We also found that poor activation of the orbitofrontal region during the task was modestly associated with a larger number of hospitalizations. The frequent number of hospitalizations was predicted by the high scores of psychotic symptoms, as well as male sex and younger age (Roick et al., 2004), and were related to social networks including relatives, friends, and mental health services (Holmes-Eber et al., 1990). This suggests that a larger number of hospitalizations is associated with more severe psychosis and poorer social connection, but this finding should be cautiously interpreted because the distribution for six hospitalizations and fewer was different from the distribution for more than six hospitalizations in the present study. However, blunted activation of the orbital frontal region may reflect illness severity and social isolation that lead to more frequent

hospitalizations in patients with SZ.

Combined with earlier findings, the results of our study suggest that aberrant activation of the superior and orbitofrontal and middle temporal regions are involved in the interaction between negatively emotional facial processing and cognitive inhibition, which is thought to underlie the pathophysiology of brain abnormalities in patients with SZ.

4.3 Abnormal behavioral performance in schizophrenia

Facial emotion discrimination studies have suggested that patients with SZ have difficulty rejecting non-target emotions and fail to correctly identifying the target emotion (Habel et al., 2010; Schneider et al., 2006; Seiferth et al., 2009). Although the task design in prior studies were not the same as the one used here, our result that patients with SZ had a higher false alarm error rate than healthy subjects during the emotional go/no-go task is in agreement with the facial emotion perception deficits of SZ. Our finding that the higher false alarm error rate in patients with SZ during the emotional task was negatively correlated with GAF scores also supports the hypothesis of impaired emotional cognitive interaction related to poor social functioning (Park et al., 2008) and negative symptoms (Chan et al., 2010). As such findings were not observed in the emotional verbal go/no-go task (Vercammen et al., 2012), the impairment in rejecting non-target emotions

may be a characteristic of patients with SZ, which may lead to inappropriate or even delusional interpretation when the patients look at emotional faces of other people. Speculatively, this could result in decreased social interaction and withdrawal.

4.4 Limitations

We should mention some limitations of the study. First, patients with SZ were medicated during study participation, which may have affected the results. However, subjects at risk of psychosis (Seiferth et al., 2008) and unmedicated, unaffected siblings of SZ patients (Kee et al., 2004) have been shown to exhibit emotional perception deficits. Medicated patients did not differ from unmedicated patients regarding their behavioral performance of facial emotion perception in a meta-analysis (Kohler et al., 2010). The present study showed that CPZ-eq was not correlated with brain activation or task performance. Therefore, the medication likely affected the results of this study to some extent, but this effect is not likely to be significant. Secondly, we did not assess participant attention during the tasks using measurements such as sleepiness and fatigue scales, although we consistently observed the subjects while they performed the tasks. Still, subjective scales should be used in future studies. Thirdly, we did not evaluate the behavioral and fNIRS data in the control block (the geometric sensorimotor go/no-go task). Some functional neuroimaging studies have demonstrated that patients with SZ exhibit deficits on this task

(Arce et al., 2006; Kaladjian et al., 2007; Kiehl et al., 2000), whereas others did not (Laurens et al., 2003; Nishimura et al., 2011). As the control block in the current study was designed as a baseline task with a larger number of tasks per trial (108 stimuli) than that in non-emotional or emotional block (32 stimuli per trial), the behavioral and fNIRS data in the control block cannot be directly compared to those in the non-emotional or emotional block. If the difference in cognitive inhibition, emotional face processing, and the interaction of the two were to be assessed in a future investigation, a different study design would be required. Fourthly, the results should be cautiously interpreted because other brain regions that cannot be measured with fNIRS may be abnormally activated, which may impact on the fronto-temporal activation in patients with SZ. Prior fMRI studies demonstrated that patients with SZ showed abnormal function of the amygdala (Hall et al., 2008; Holt et al., 2006; Li et al., 2010) and parahippocampus (Li et al., 2010; Surguladze et al., 2006) during an emotional and neutral face task, and the anterior cingulate was abnormally activated during an emotional Stroop task (Park et al., 2008). The amygdala is a key player in emotional face processing (Haxby et al., 2000) and is activated in the emotional go/no-go task (Hare et al., 2008). The anterior cingulate connects with the dorsolateral and middle frontal regions and orbitofrontal cortex and is known to be involved in aspects of working memory, rule-based learning, attention, and

emotional regulation (Bonelli et al., 2007). fNIRS cannot detect the activation of these regions because they are located deep in the brain; thus, the activation of these regions may have affected brain function and behavioral performance in the present study. Finally, as NIRS has a low spatial resolution (approximately 3 cm, which is roughly 1 gyrus of the brain) (Suda et al., 2011), anatomical identification in the present study is not as accurate as fMRI investigations.

5. Conclusion

This is the first fNIRS study to evaluate brain function during an emotional go/no-go task in patients with SZ. Our results suggest that patients with SZ exhibit blunted fronto-temporal activation in response to the interaction task, suggesting that dysfunction of these brain regions is involved in the pathophysiology of abnormal emotional processing and cognitive inhibition in patients with SZ. These findings may further our understanding of impaired social interaction in patients with SZ.

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Figure legends

Figure 1. Task design of the emotional go/no-go task in fNIRS.

Each block included two variations of facial information discrimination (E1 and E2 in the emotional block, NE1 and NE2 in the non-emotional block). The target stimuli for Go differ in each task. For example, in the emotional block, angry and fearful faces are the target stimuli of the E1 and E2 tasks, respectively. All of the blocks are 404 s.

C, Control task; E, Emotional task; NE, Non-emotional task.

Figure 2. Within-group comparison of mean [oxy-Hb] changes during the emotional and non-emotional go/no-go blocks in patients with SZ and healthy subjects.

A: Red traces indicate [oxy-Hb] during the emotional block, and pink traces indicate [oxy-Hb] during the non-emotional block in healthy subjects. Orange boxes show channels with significant mean [oxy-Hb] changes between the emotional and non-emotional go/no-go blocks in healthy subjects. B: Blue traces indicate [oxy-Hb] during the emotional blocks, and turquoise trace indicate [oxy-Hb] during the non-emotional blocks in patients with SZ. C: Orange circles with the channel number represent the location of the channels with significance in A, and white circles represent the location of non-significant channels.

Figure 3. Between-group comparison of mean [oxy-Hb] changes during the emotional go/no-go blocks between patients with SZ and healthy subjects.

A: Red traces indicate [oxy-Hb] in healthy subjects, and blue traces indicate [oxy-Hb] in patients with SZ during the emotional go/no-go block. Orange boxes show channels with significantly different mean [oxy-Hb] changes during the emotional blocks between patients with SZ and healthy subjects. B: Orange circles with the channel number represent the location of the channels with significance in A, and white circles represent the location of non-significant channels.

Table 1. Demographic and clinical characteristics of participants.

	Healthy (n = 28)	Schizophrenia (n = 25)	*p*
Age (years)	40.1 ± 8.1	41.3 ± 9.2	0.62
Sex (m/f)	12/16	10/15	0.83
Educations (years)	15.9 ± 2.1	13.4 ± 2.3	<0.001
[a] Handedness	86.1 ± 18.1	79.6 ± 39.3	0.44
[b] Estimated premorbid IQ	102.0 ± 6.4	99.4 ± 10.8	0.28
DUP (months)	-	14.6 ± 30.3	
Duration of illness (years)	-	21.5 ± 11.0	
PANSS five-factor model			
Positive factor	-	6.6 ± 3.0	
Negative factor	-	18.7 ± 7.7	
Disorganized/concrete factor	-	5.1 ± 2.6	
Excited factor	-	4.8 ± 2.6	
Depressed factor	-	4.0 ± 1.5	
GAF	-	47.8 ± 17.9	
CPZ-eq (mg/day)	-	981.6 ± 589.7	

DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; CPZ-eq, chlorpromazine-equivalents

Data were given as mean ± sd. [a] Assessed using the Edinburgh Handedness Inventory.

[b] Assessed using the Japanese version of the National Adult Reading Test.

$p < 0.01$ by Student's t-test

Table 2. Behavioral performance in the emotional and non-emotional blocks

	Healthy	Schizophrenia
Emotional task		
Reaction time (ms)	632.0 ± 121.3	803.4 ± 155.6
False alarm error (%)	4.7 ± 8.6	19.8 ± 23.6
Omission error (%)	10.5 ± 13.5	18.5 ± 17.1
Non-emotional task		
Reaction time (ms)	530.7 ± 79.0	622.6 ± 104.8
False alarm error (%)	2.0 ± 3.0	4.5 ± 6.4
Omission error (%)	0.7 ± 2.6	4.0 ± 5.7

Table 3. Emotional vs. non-emotional blocks in healthy subjects

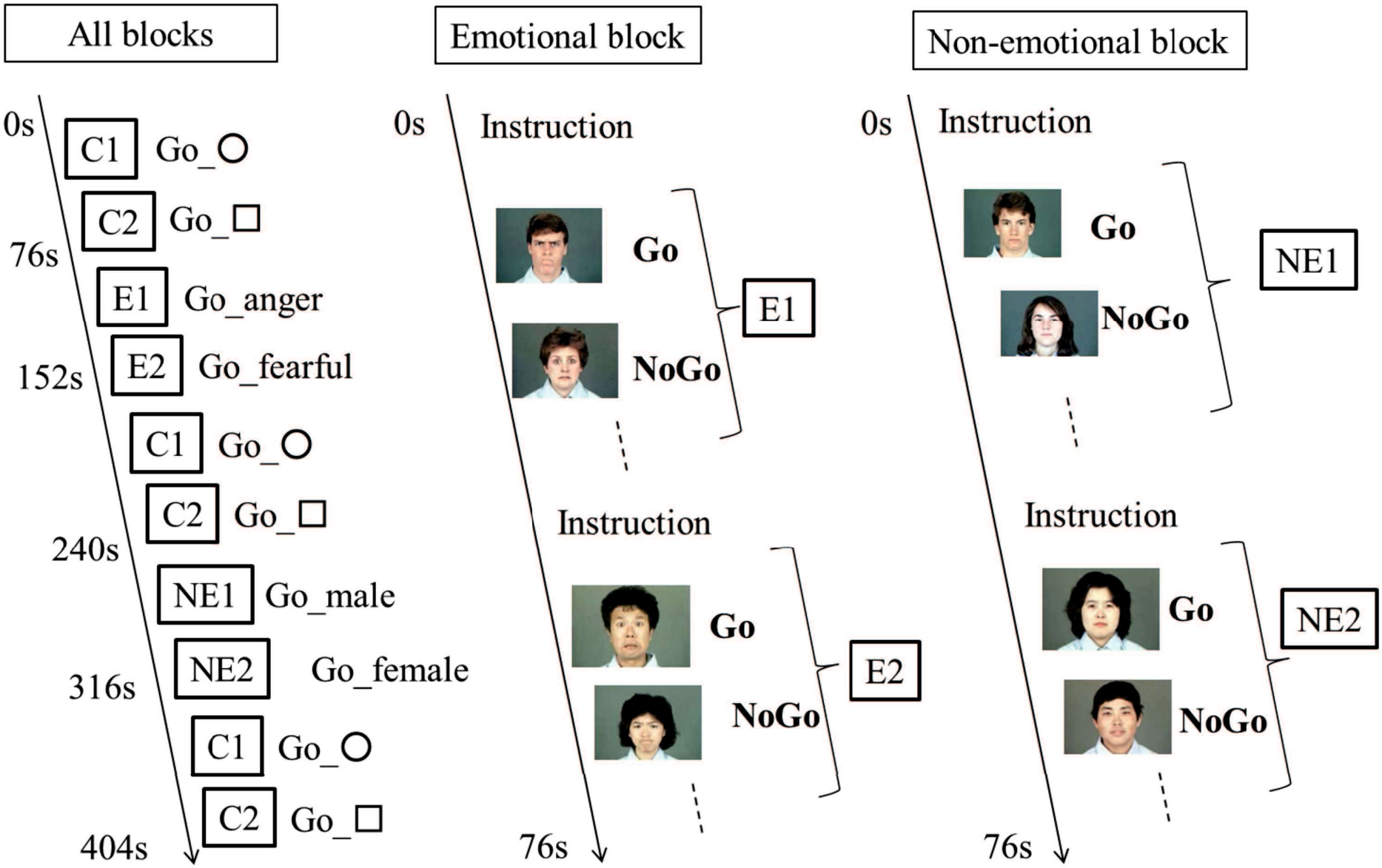
Channel #	Estimated region	Emotional	Non-emotional
[oxy-Hb]			
29	Left inferior frontal region	0.11 ± 0.19	0.01 ± 0.08
37	Left superior medial frontal region	0.12 ± 0.18	0.01 ± 0.11
38	Left superior frontal region	0.12 ± 0.15	0.02 ± 0.09
39	Left middle frontal region	0.14 ± 0.20	0.04 ± 0.13
46	Right middle orbitofrontal region	0.13 ± 0.19	0.03 ± 0.12
48	Left middle orbitofrontal region	0.12 ± 0.16	0.02 ± 0.13
49	Left middle orbitofrontal region	0.11 ± 0.15	0.03 ± 0.10
[deoxy-Hb]			
47	Right superior orbitofrontal region	-0.04 ± 0.06	-0.01 ± 0.04

The values are the mean ± sd (mmol·mm).

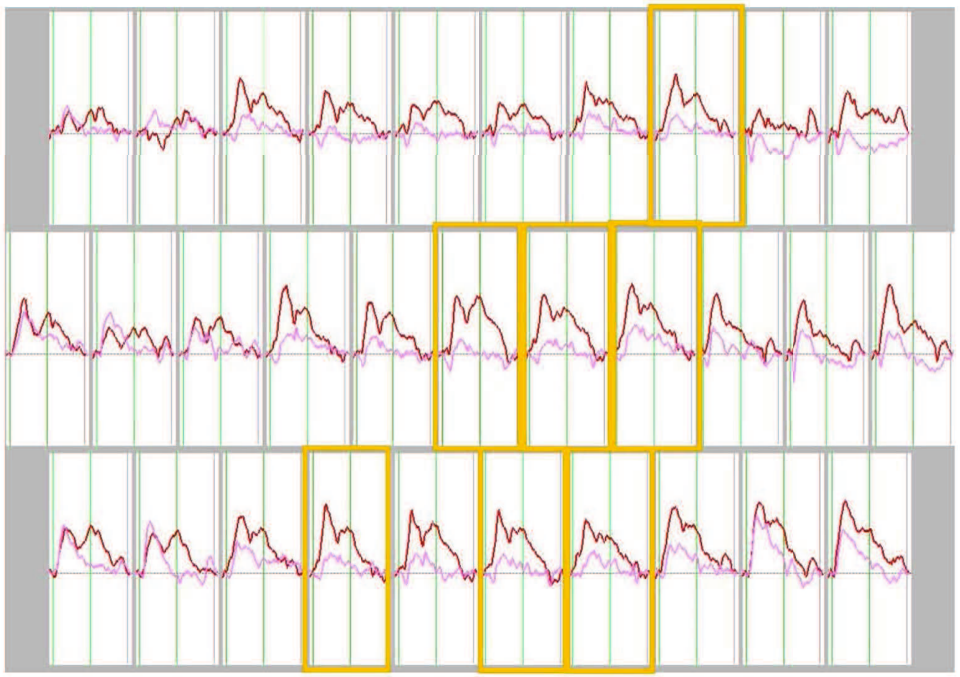
Table 4. Schizophrenia vs. healthy subjects in the emotional block

Channel #	Estimated region	Schizophrenia	Healthy
[oxy-Hb]			
37	Left superior medial frontal region	-0.02 ± 0.13	0.12 ± 0.18
38	Left superior frontal region	-0.02 ± 0.08	0.12 ± 0.15
42	Left middle temporal region	0.03 ± 0.08	0.11 ± 0.09
47	Right superior orbitofrontal region	-0.01 ± 0.11	0.11 ± 0.19
48	Left middle orbitofrontal region	-0.01 ± 0.09	0.12 ± 0.16
[deoxy-Hb]			
39	Left middle frontal region	0.003 ± 0.04	-0.04 ± 0.05

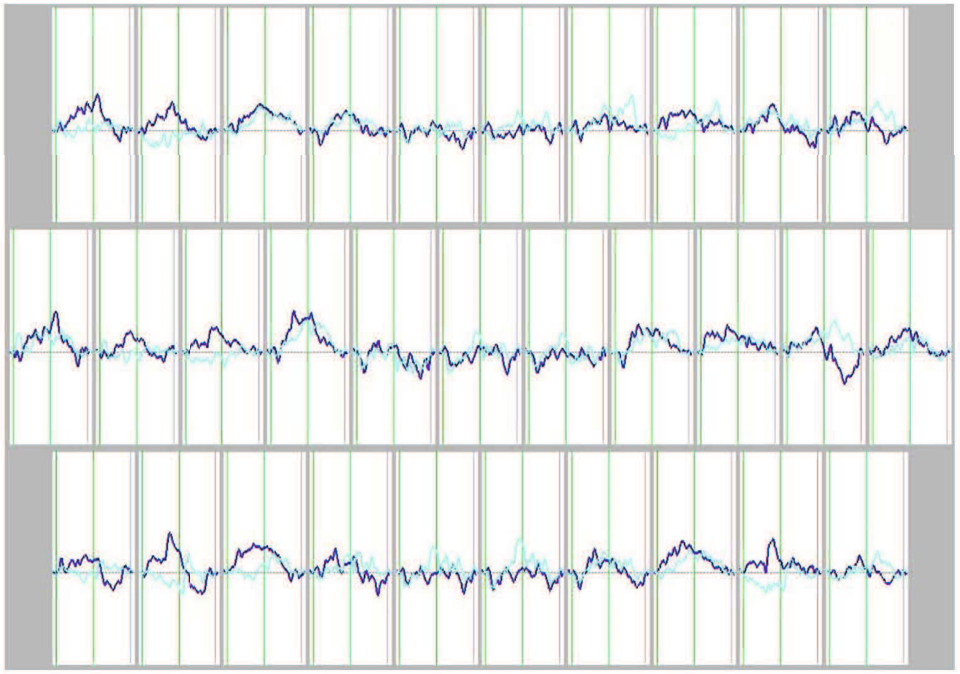
The values are the mean ± sd (mmol·mm).


All blocks
0s
C1
Go_○
C2
Go_□
76s
E1
Go_anger
E2
Go_fearful
152s
C1
Go_○
C2
Go_□
240s
NE1
Go_male
NE2
Go_female
316s
C1
Go_○
C2
Go_□
404s
Emotional block
0s
Instruction
Go
NoGo
E1
Instruction
Go
NoGo
E2
76s
Non-emotional block
0s
Instruction
Go
NoGo
NE1
Instruction
Go
NoGo
NE2
76s

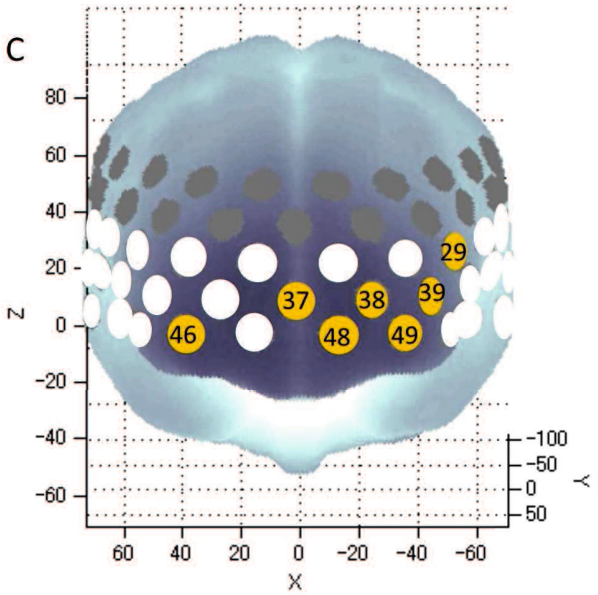
A



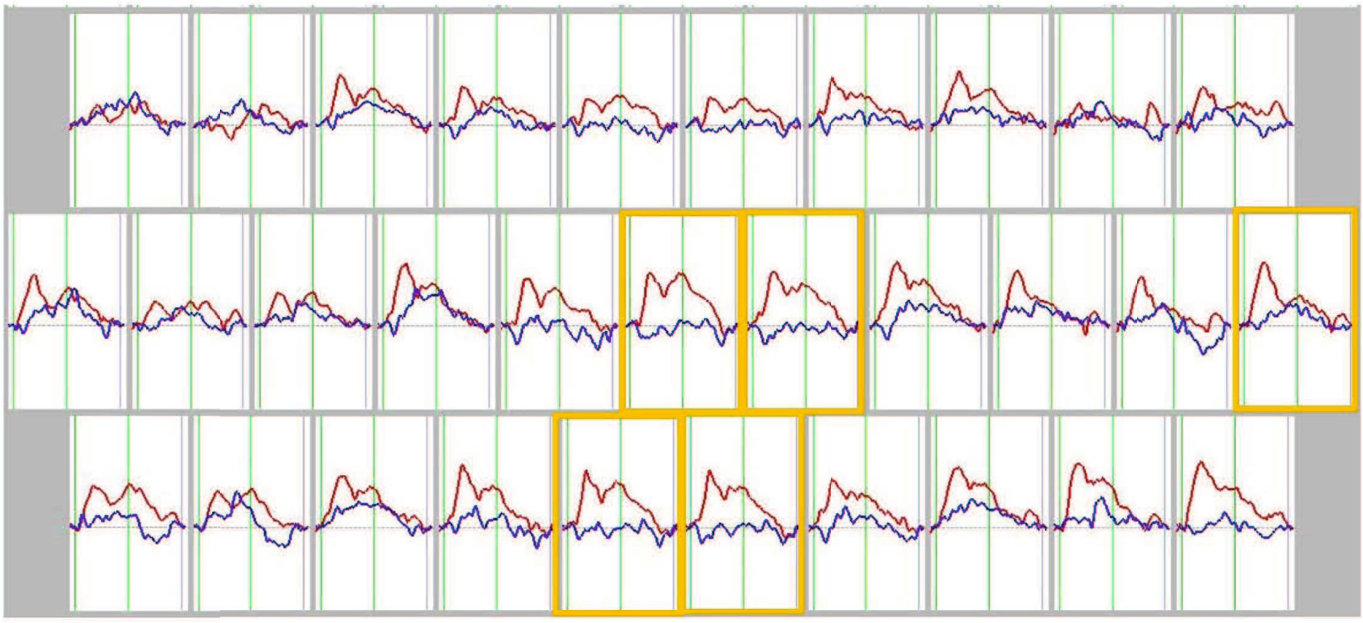
B



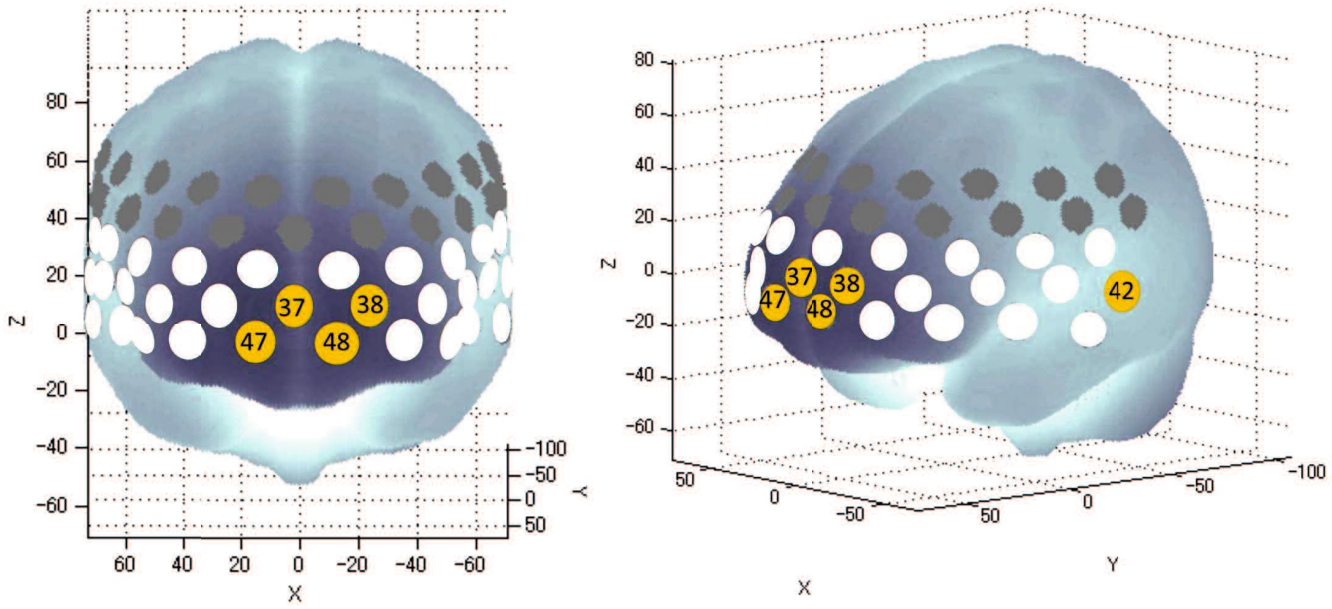
C


80
60
40
20
0
-20
-40
-60
Z
29
37
38
39
46
48
49
60
40
20
0
-20
-40
-60
X
-100
-50
0
50
Y

A



B


80
60
40
20
0
-20
-40
-60
Z
37
38
47
48
60
40
20
0
-20
-40
-60
X
-100
-50
0
50
Y
42
-50
0
50
-100