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鈴木道雄	統合失調症の早期介入と脳画像診断	日本精神科病院協会雑誌	29	35-40	2011
鈴木道雄，高橋　努，川崎康弘，中村主計，高柳陽一郎	統合失調症における脳の構造画像マーカー	精神科	18	506-512	2011
高橋 努，鈴木道雄	早期精神病における脳形態変化	日本生物学的精神医学会誌	22	15-20	2011
高橋 努，鈴木道雄	特集「精神科領域における画像診断の展望」統合失調症圏のMRI研究	最新精神医学	16	269-273	2011
野田隆政	光トポグラフィーによるうつ病診断補助の現状.	Depression Frontier	9	94-101	2011
野田隆政，樋口輝彦.	特集気分障害－季節の変わり目に出現しやすいうつ病の診断と治療　気分障害研究の最前線　光トポグラフィー検査の有用性.	カレントテラピー	29	43-47	2011
野田隆政	精神疾患の診断ツールとしてのNIRS測定	精神科	18	528-534	2011

Ⅳ．　研究成果の刊行物・別刷

Autistic Traits and Brain Activation during Face-to-Face Conversations in Typically Developed Adults

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Abstract

Background: Autism spectrum disorders (ASD) are characterized by impaired social interaction and communication, restricted interests, and repetitive behaviours. The severity of these characteristics is posited to lie on a continuum that extends into the general population. Brain substrates underlying ASD have been investigated through functional neuroimaging studies using functional magnetic resonance imaging (fMRI). However, fMRI has methodological constraints for studying brain mechanisms during social interactions (for example, noise, lying on a gantry during the procedure, etc.). In this study, we investigated whether variations in autism spectrum traits are associated with changes in patterns of brain activation in typically developed adults. We used near-infrared spectroscopy (NIRS), a recently developed functional neuroimaging technique that uses near-infrared light, to monitor brain activation in a natural setting that is suitable for studying brain functions during social interactions.

Methodology: We monitored regional cerebral blood volume changes using a 52-channel NIRS apparatus over the prefrontal cortex (PFC) and superior temporal sulcus (STS), 2 areas implicated in social cognition and the pathology of ASD, in 28 typically developed participants (14 male and 14 female) during face-to-face conversations. This task was designed to resemble a realistic social situation. We examined the correlations of these changes with autistic traits assessed using the Autism-Spectrum Quotient (AQ).

Principal Findings: Both the PFC and STS were significantly activated during face-to-face conversations. AQ scores were negatively correlated with regional cerebral blood volume increases in the left STS during face-to-face conversations, especially in males.

Conclusions: Our results demonstrate successful monitoring of brain function during realistic social interactions by NIRS as well as lesser brain activation in the left STS during face-to-face conversations in typically developed participants with higher levels of autistic traits.

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Introduction

Autism is a developmental disorder characterized by impaired social interactions and communication in addition to restricted and repetitive behaviour. In recent years, the concept of autism spectrum disorders (ASD) has been proposed; it hypothesizes a wide range of symptoms resembling autism, such as those demonstrated in Asperger syndrome and pervasive developmental disorder not otherwise specified. According to this concept, disorders across the spectrum are believed to have common biological bases. Postmortem and structural magnetic resonance imaging (MRI) studies have highlighted the prefrontal cortex (PFC), including the medial PFC, the superior temporal sulcus (STS), the amygdala, the anterior cingulate cortex, the fusiform gyrus, the thalamus, and the cerebellum as pathological substrates for ASD [1].

Many functional neuroimaging studies of ASD focusing on impaired social interactions and communication have been conducted using functional MRI (fMRI). By employing task stimuli related to social cognitive modules, such as face recognition, visual motion processing, the theory of mind, and eye-gaze perception, these studies have implicated several brain regions in the pathogenesis of autism, including the STS and the fusiform gyrus for face processing [2,3]; the PFC, including the medial prefrontal cortex, for mentalising and person perception [4,5]; the temporoparietal junction [6]; and the amygdala for threat detection, emotion recognition, and complex social judgments [7,8]. Moreover, these studies have provided a foundation for understanding neural mechanisms underlying social deficits in ASD. However, fMRI has methodological constraints for studying brain mechanisms underlying social

cognition. For example, participants are required to lie on a bed in a small, noisy gantry during examination, a condition that is upsetting to many people, including those with autism. Due to this limitation, most previous studies have necessarily been conducted in an unusual and unrealistic way, such as using pictures or computer graphics images shown on a computer monitor as task stimuli. A functional brain imaging methodology that enables monitoring of brain activation in a more natural setting might well offer more informative data from more realistic social interactive situations, such as having an interview with another person, which is impossible with fMRI because of its methodological constraints.

Near-infrared spectroscopy (NIRS) is a recently developed functional brain imaging technique that involves emission of near-infrared light that can be detected through the scalp [9]. NIRS allows monitoring of cerebral blood volume (CBV) changes in the neocortex as indicated by increased oxygenated haemoglobin concentrations ([oxy-Hb]) and decreased deoxygenated haemoglobin concentration ([deoxy-Hb]) using a small apparatus, although certain measurement concerns remain, such as the effect of blood flow in the scalp or the difficulty in determining the exact length of the light path for each subject. NIRS has some methodological limitations as well, such as a low spatial resolution (approximately 3 cm, which is nearly equal to 1 gyrus of the brain) and an inability to assess deep brain structures. Nevertheless, when an NIRS probe is placed on the head in one of the 10–20 standard electroencephalography electrode positions, the cerebrocranial correlation is considered to vary within 1 cm; therefore, correspondence at the level of the gyrus is not affected [10].

Despite these methodological limitations, NIRS enables brain activity measurement in a more natural setting compared with other functional brain imaging techniques. Subjects can undergo NIRS examination in a seated position, with their eyes open, while speaking, and without any noise or pain. These characteristics of NIRS are considered to be particularly suitable for social interaction studies. Thus far, NIRS has successfully been demonstrated for monitoring brain function in healthy participants during delicate and/or subjective experiences, such as subjective sleepiness and psychological fatigue [11,12] and in patients with psychiatric disorders who are sensitive to the experimental environment [13–16]. In short, NIRS has certain distinct advantages, such as complete non-invasiveness, lack of restriction of body movement, and the small size of the apparatus, but it is not able to detect signals within the deep brain structure and has a low spatial resolution of approximately 1 gyrus.

In this study, we used NIRS to monitor brain activation in healthy seated participants during conversations to examine social cognition in a natural setting. Such an approach may further our understanding of brain activity during social interactions in everyday life and of associations between multiple social cognitive modules in realistic situations. We further investigated the relationship between brain activation in the PFC and STS regions during face-to-face conversations and, because the severity of characteristics of ASD is posited to lie on a continuum that extends into the general population, we evaluated autistic traits in typically developed adults [17,18]. To determine the extent to which adults of average intelligence display characteristics associated with ASD, Baron-Cohen et al. developed a self-administered questionnaire, the Autism-Spectrum Quotient (AQ) [19]. We hypothesized that face-to-face conversations would activate the PFC as well as the STS (since both areas are involved in social cognition) and that variations in autistic traits in the typically developed participants would be correlated with brain activation during face-to-face conversations.

Methods

Participants

Twenty-eight healthy volunteers participated in this study (14 males and 14 females; average age, 26.4 years; standard deviation [SD], 3.0; range, 23–35). The participants in this study were medical interns at Gunma University Hospital and students at Gunma University Faculty of Medicine. All were right-handed and had no history of any major psychiatric disorder, autism, neurological disorder, substance abuse, head injury, or major physical illness. Moreover, they were not on any psychotropic medications at the time of the study. These participants had also been included in our previous study [16], and their autistic traits were assessed using the Japanese version of the AQ [19,20]. This study was approved by the Institutional Review Board of the Gunma University Graduate School of Medicine. Written informed consent was obtained from all participants prior to the study.

Activation Task

We employed 2 types of activation tasks: a conversation condition and a control condition. The order of the 2 tasks was counterbalanced among the participants. The participants sat on comfortable chairs in a room throughout the measurement process (Figure 1). Direct sunlight was shut out by a curtain.

Conversation condition. The task was designed to simulate ordinary conversations in everyday life, albeit in an experimental setting. Each participant and an interviewer sat face to face 1 m apart on comfortable chairs in a sunlit room with their eyes open, and the NIRS probes were placed on the participant's frontal and temporal regions. Before beginning and after finishing the experiment, the participant and the interviewer were separated by a partition so that they could not see each other. The partition was removed during the experiment.

The experiment consisted of 3 periods: pre-task, task, and post-task. During the task period, the participant was required to talk with the interviewer in front of them. To avoid qualitative and quantitative differences among the conversations, the participants were instructed to make conversation during the task period in accordance with the following 2 criteria. First, the time course of the conversation was settled a priori: the subject and the interviewer were to speak in turn, in that order, every 15 s; this was accomplished via verbal cues from the experimenter every 5 s. The task period consisted of 6 30-s conversation cycles, with the entire conversation lasting as long as 180 s. Second, the theme of the conversation was limited to anything related to food. The theme of the conversation was limited to food because in initial experiments to test the conversational task, this was one of the most popular topics among all of the participants and was relatively easy to discuss with a person upon meeting for the first time. The interviewers were 3 male psychiatrists who were not acquainted with the participants. During the pre-task and post-task periods, the participants were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ (the Japanese counterparts of English vowel sounds) to exclude the effect of phonation and stabilize the baseline conditions. Using videotape, the images and voices of the subjects and interviewers were recorded during the experiment for further analysis.

Task performance during the conversation was evaluated in 3 ways. First, the amount of discussion by the participants was evaluated quantitatively as speaking time, which corresponded to the length of the participants' speech measured using the recorded videotape. Second, the content of the conversation was evaluated qualitatively in terms of receiving and sending aspects. The

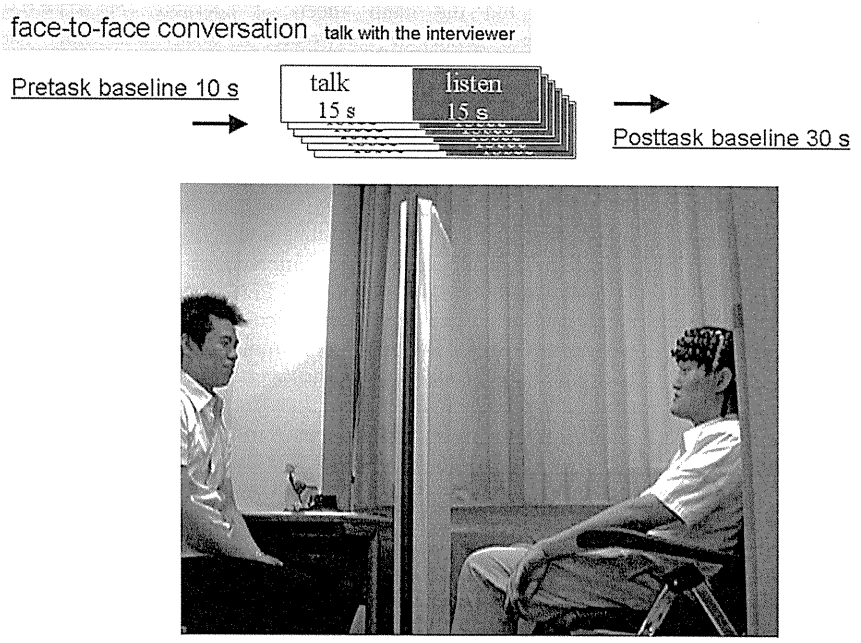

Figure 1. Task procedures and setting. The participants were required to talk with the interviewer seated in front of them during the task segment, in which they faced each other and sat on chairs. The task period consisted of 6 cycles of a 30-s conversation, with total conversations as long as 180 s. Before beginning and after finishing the task, the participant and the interviewer were separated by a partition so that they could not see each other; during the experiment itself, the partition was removed. As shown in the photograph, the participant wearing the near-infrared spectroscopy probe on his forehead sat on the right, whereas the interviewer sat on the left.
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receiving aspect (RS) indicated the appropriateness of the response within the context of the conversation: the subject's replies to the preceding statements by the interviewer were scored as (1) appropriate, (2) partially appropriate, (3) partially inappropriate, and (4) inappropriate. The sending aspect (SS) indicated the productivity of new topics: the subject's questions to the interviewer were scored as (1) a completely new topic, (2) a partially new topic, (3) nearly the same topic, and (4) not a new topic. Third, the expressiveness of the subjects was evaluated by observation according to the Broader Phenotype Autism Symptoms Scale [21]. Expressiveness consists of 4 dimensions: eye gaze (an individual's eye contact both when listening and speaking or when otherwise interacting with the examiner), social smiling (an individual's response to the examiner's smiles), facial expressions (the range and appropriateness of facial expressions), and prosody (whether an individual exhibits atypical rate, rhythm, volume, and/or intonation of speech). Each dimension was scored as (1) normal, average, or typical functioning for a person of that age and life circumstance; (2) on the lower end of the average range or somewhat lower than most people, but not significantly impaired; (3) outside the normal range, definitely below average, or impaired; or (4) far outside the normal range, well below average, or significantly impaired.

Control condition. To examine brain activation and artefact contamination induced by phonation only, a control task was conducted in addition to the experimental task. The subjects were instructed to repeat meaningless syllables such as 'a', 'ka', 'sa', 'ta', and 'na' during their turns to speak in the task period. All subjects were able to repeat such syllables without interruption.

Near-infrared Light Spectroscopy Measurement

In this study, changes in [oxy-Hb] and [deoxy-Hb] were measured using a 52-channel (Ch) NIRS machine (Hitachi ETG-4000). Absorption at 2 wavelengths of near-infrared light (780 and 830 nm) was measured, from which [oxy-Hb] and [deoxy-Hb] were calculated, respectively. As an index of CBV changes, [oxy-Hb] changes were evaluated. The distance between the pairs of emission and detector probes was 3.0 cm, and the machine was considered to measure depths of 2–3 cm below the scalp; that is, at the surface of the cerebral cortex [22,23].

The probes of the NIRS machine were placed on the participant's frontal region (Figure S1 online). The frontal probes measured [Hb] changes at 52 measurement points over a 6×30-cm area. We used a 3×11 probe holder for the Hitachi ETG-4000 with 17 light sources and 16 light detectors, with the lowest probes positioned along the Fp1–Fp2 line, in accordance with the international 10/20 system used in electroencephalography.

Absorption of near-infrared light was measured at a time resolution of 0.1 s. The obtained data were analyzed using the 'integral mode'. The pre-task baseline was determined as the mean of the last 10 s of the 30-s pre-task period, the post-task baseline was determined as the mean of the last 10 s of the 30-s post-task period, and linear fitting was applied to the data between these 2 baselines. The moving average method was used to exclude short-term motion artefacts in the analyzed data (moving average window: 5 s).

Data Analyses

The dependence of autistic traits on the participants' age and gender was examined using multiple regression analyses employing the AQ score as a dependent variable and age and gender as independent variables. The relationship between autistic traits and task performance during face-to-face conversations was also examined using multiple regression analyses employing 3 indices of task performance as dependent variables: speaking time, the score for qualitative evaluation of the RSs, and the score for

qualitative evaluation of the SSs. AQ score, age, and gender were the independent variables.

The waveforms of [Hb] changes for all 52 Chs under conversation and control conditions were calculated for all participants. NIRS data from Chs that clearly contained artefacts, as determined by close observation of the subjects (Chs 1–21), were excluded from further analyses. The most common cause of these artefacts was NIRS probe drift due to the presence of hair. Probes placed on an area with a lot of hair are difficult to adequately fasten onto the head and can be easily displaced.

First, the average [Hb] changes during the 2 tasks in the 4 regions of interest were calculated: right PFC (Chs 25, 26, 35, 36, and 47), right STS (Chs 22, 32, 33, 43, and 44), left PFC (Chs 27, 28, 38, 39, and 48), and left STS (Chs 31, 41, 42, 51, and 52). These were identified in accordance with correspondences between the NIRS Chs and measurement points on the cerebral cortex as determined by the virtual registration method in which structural information from an anatomical database is used to obtain estimates of Ch positions in a standardized stereotaxic 3D brain atlas (Figure S1 online) [24]. There were 3 light sources and 3 detectors in the PFC, and 3 light sources and 2 detectors in the STS. Averaged [oxy-Hb] changes during the 180-s task segment across 5 Chs in each of 4 regions were analyzed by four-way repeated-measures analysis of covariance (ANCOVA) with task (conversation or control) and gender as the inter-individual independent variables, laterality (right or left) and region (PFC or STS) as the intra-individual independent variables, and age as the covariate. This was followed by post hoc *t*-tests. We analyzed age as the covariate because [oxy-Hb] changes over the frontal lobe during a cognitive task were significantly correlated with age in our previous NIRS study [14].

We then investigated the relationship between [Hb] changes during face-to-face conversations and autistic traits of the participants. A simple correlation of [Hb] changes under conversation and control conditions in the 4 regions of interest with AQ score was conducted. In addition, the relationships between [Hb] changes and autistic traits by gender were analyzed to test a theory described by Baron-Cohen as 'extreme male brain', which attempts to account for differences in autistic traits between the 2 genders [25].

Finally, we investigated relationships between activation in the 4 regions of interest. Simple correlations were examined between regional CBV changes among the 4 regions of interest, right PFC, right STS, left PFC, and left STS, among all the participants and by gender.

Results

Characteristics of Participants and Behavioural Data

The AQ scores and task performances of the participants are shown in Table S1 (online). An AQ cut-off score of ≥32 is often used to identify a person as having autism; in the present study, 1 subject scored 33 (subject no. 14, Table S1 online). Task performances during the face-to-face conversations were not correlated with AQ scores, age, or gender, and the AQ scores were not significantly correlated with age or gender.

[Hb] Changes during Face-to-Face Conversations

Average [oxy-Hb] changes during the 180-s task segment and grand-averaged waveforms across 5 Chs in 4 regions are shown in Figure 2. The average [oxy-Hb] changes during the 180-s task segment in 4 regions are shown in Table 1. Four-way repeated-measures ANCOVA showed that the main effects of the task ($F[1,51] = 59.7$, $P<0.001$) and region ($F = 6.2$, $P = 0.016$) were significant, but the main effects of laterality ($F[1,51] = 0.9$, $P = 0.33$) and gender ($F[1,51] = 0.7$, $P = 0.42$) were not. The significant main effects of task and region indicate significantly greater [oxy-Hb] increases under the conversation condition than under the control condition, and significantly greater [oxy-Hb] increases in the PFC than in the STS. Four-way repeated-measures ANCOVA also showed significant two-way interactions of task by region ($F[1,51] = 13.3$, $P = 0.001$) and task by gender ($F[1,51] = 5.1$, $P = 0.028$); the other interactions were not significant. These significant two-way interactions indicate that [oxy-Hb] increased predominantly in the PFC under the conversation condition but not under the control condition. In addition, there were greater [oxy-Hb] increases in males than in females under the conversation condition, but the reverse was observed under the control condition.

The average [deoxy-Hb] changes during the 180-s task segment in 4 regions are shown in Table 1. Four-way repeated-measures ANCOVA showed a significant main effect of the task ($F[1,51] = 6.3$, $P = 0.016$), but did not show any other significant main effects or interactions. The main effect of task indicates significantly greater [deoxy-Hb] decreases under the conversation condition than under the control condition.

Relationships between Brain Activation and AQ Scores

Correlations between AQ scores and [oxy-Hb] changes under the conversation condition in the 4 regions of interest are shown in Table 2. AQ scores were correlated with [oxy-Hb] changes in the left STS (rho = −0.460, $P = 0.01$; Figure 3a) but not with the other regions under the conversation condition. There were no significant correlations between [oxy-Hb] changes and AQ scores under the control condition.

Although the communication subscore correlated with [oxy-Hb] changes in the left STS under the conversation condition (rho = −0.429, $P = 0.02$), the correlation was no longer significant after Bonferroni correction for multiple correlations. The corrected significance level was set at $P<0.0125$ based on the following rationale: we excluded the 16 [deoxy-Hb] comparisons from the requisite Bonferroni divisor; physiologically, it is understood that the cerebrovascular response exerts a much lesser effect on [deoxy-Hb] than on [oxy-Hb]. The 4 remaining control-task comparisons were excluded on the basis of prior expectation of an effect only in the conversation task.

AQ scores were significantly correlated with [oxy-Hb] changes in the left STS in male participants (rho = −0.730, $P = 0.003$; Figure 3b) but not in female participants (rho = −0.434, $P = 0.12$) under the conversation condition (after Bonferroni correction for multiple correlations, $P<0.006$). However, there was no significant difference between the 2 coefficients of correlation ($X^2 = 1.8161$, df = 1, $p = 0.1778$).

Associations between Activation in the 4 Regions of Interest

For [ox-Hb] changes during face-to-face conversation, there was only 1 significant correlation between the right PFC and left PFC ($r = 0.927$, $p<0.001$); the other correlations were not significant after Bonferroni correction for multiple correlations ($P<0.008$). In males, there was only 1 significant correlation between the right PFC and left PFC ($r = 0.941$, $p<0.001$), similar to the mixed group. However, in females, there were additional significant correlations between the left STS and right PFC ($r = 0.716$, $p = 0.004$) and the left STS and left PFC ($r = 0.682$, $p = 0.007$), in addition to the right PFC and left PFC ($r = 0.890$, $p<0.001$). These results indicate that there were strong positive correlations between bilateral PFC activations during conversa-

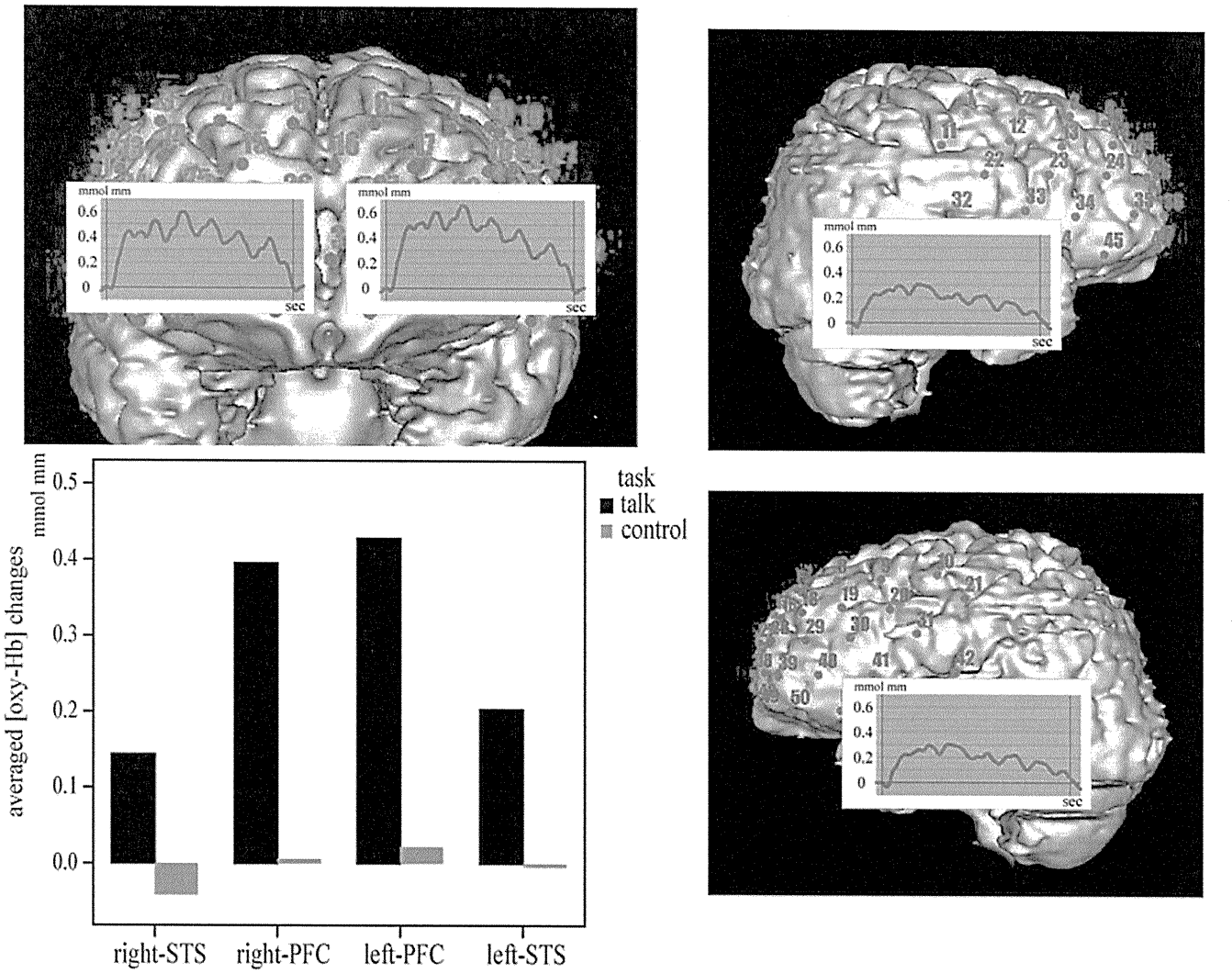

Figure 2. Grand-averaged waveforms of oxygenated haemoglobin concentrations ([oxy-Hb]) under task and control conditions. Grand-averaged waveforms of [oxy-Hb] under conversation conditions (red line) and during the entire 180-s task segment (between each pair of vertical lines) under conversation conditions (black bar) and control conditions (gray bar) as measured by near-infrared spectroscopy in 4 regions of interest: right prefrontal cortex (PFC), right superior temporal sulcus (STS), left PFC, and left STS.
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tion; however, in females, there were additional positive correlation between left STS activation and PFC activation. For [oxy-Hb] changes under control conditions, there was only 1 significant correlation between the right PFC and left PFC (mixed group: $r = 0.862$, $p < 0.001$; males: $r = 0.864$, $p < 0.001$; females: $r = 0.854$, $p < 0.001$); the other correlations were not significant.

For [deoxy-Hb] changes, there was only 1 significant correlation between the right PFC and left PFC (mixed group: $r = 0.658$,

Table 1. Averaged [oxy-Hb] and [deoxy-Hb] changes during conversation condition and control condition.

			right STS		right PFC	left PFC	left STS
Conver.	[oxy-Hb]		0.14 (0.22)	0.40 (0.33)	0.43 (0.31)	0.20 (0.10)	
	[deoxy-Hb]	−0.05 (0.14)	−0.05 (0.14)	−0.04 (0.07)	−0.04 (0.13)		
Control	[oxy-Hb]		−0.4 (0.11)	0.01 (0.08)	0.02 (0.08)	−0.003 (0.08)	
	[deoxy-Hb]	−0.002 (0.03)	−0.003 (0.07)	0.007 (0.03)	−0.02 (0.07)		
							mean (SD)

Conver., conversation condition; Control, control condition; [oxy-Hb], oxygenated hemoglobin; [deoxy-Hb], deoxygenated hemoglobin; STS, superior temporal sulcus; PFC, prefrontal cortex.
doi:10.1371/journal.pone.0020021.t001

Table 2. Correlation between AQ score and [oxy-Hb].

AQ vs.	right STS	right PFC	left PFC	left STS
rho	−0.063	−0.17	−0.136	−.460*
P value	0.75	0.388	0.489	.014*

AQ, Autism Spectrum Quotient; oxy-Hb, oxygenated hemoglobin; STS, superior temporal sulcus; PFC, prefrontal cortex.
doi:10.1371/journal.pone.0020021.t002

$p<0.001$; males: $r=0.721$, $p=0.004$; females: not significant) during conversation; the other correlations were not significant.

Discussion

In this study, we examined brain activation during face-to-face conversations by measuring regional CBV (rCBV) increases using NIRS. The results demonstrated that 1) face-to-face conversation was accompanied by significant bilateral rCBV increases in the PFC and STS regions, with greater increases in the PFC than in the STS, 2) there were strong positive correlations between bilateral rCBV increases in the PFC in both genders, but there were additional positive correlations between left STS activation and bilateral PFC activations in females, and 3) AQ scores of typically developed (non-ASD) participants were negatively correlated with rCBV increases in the left STS region during face-to-face conversation, especially in male participants.

Conversation Performances and Autistic Traits

Task performance, i.e. the amount of speech and expression of the participants, was not correlated with autistic traits. This unexpected absence of correlation may be because only 1 subject was above the AQ cut-off. Alternatively, since all of the participants in this study were healthy and socially well-functioning subjects and were able to perform the conversation task quite easily (Table S1 online), there may have been subject selection bias. If subjects with higher AQ scores or lower levels of social functioning had been included, we might have seen significant correlations between task performance and autistic traits.

Brain Activation during Face-to-Face Conversation

Brain activation in the PFC and STS are assumed to represent the output and input aspects of conversation, respectively [26,27]. In our study, the former was greater than the latter only under face-to-face conversation conditions. Because the NIRS Chs in this study detected dorsolateral but not medial PFC activities, the obtained PFC activations are assumed to reflect executive function mediated by the dorsolateral PFC [28]. The nature of the task employed in this study may explain the greater activation in the PFC (reflecting executive functions such as planning, problem solving, and working memory) than in the STS (reflecting social cognition): the subjects were required to actively generate conversation by broaching topics and asking questions. Therefore, the greater activation in the PFC than in the STS in this study is possibly related to the task characteristics.

Based on the results of correlations among activation in the regions of interest, we speculate that the male participants may have conducted face-to-face conversation using mainly the bilateral PFC, corresponding to executive functions such as planning and problem solving. However, the female participants may have conducted face-to-face conversation using both the STS, corresponding to social cognitive function, and the PFC in a coordinated manner. These results are consistent with empirical knowledge relating to differences in conversation styles by gender; females tend to be more 'empathising' and males tend to be more 'systemising' [29].

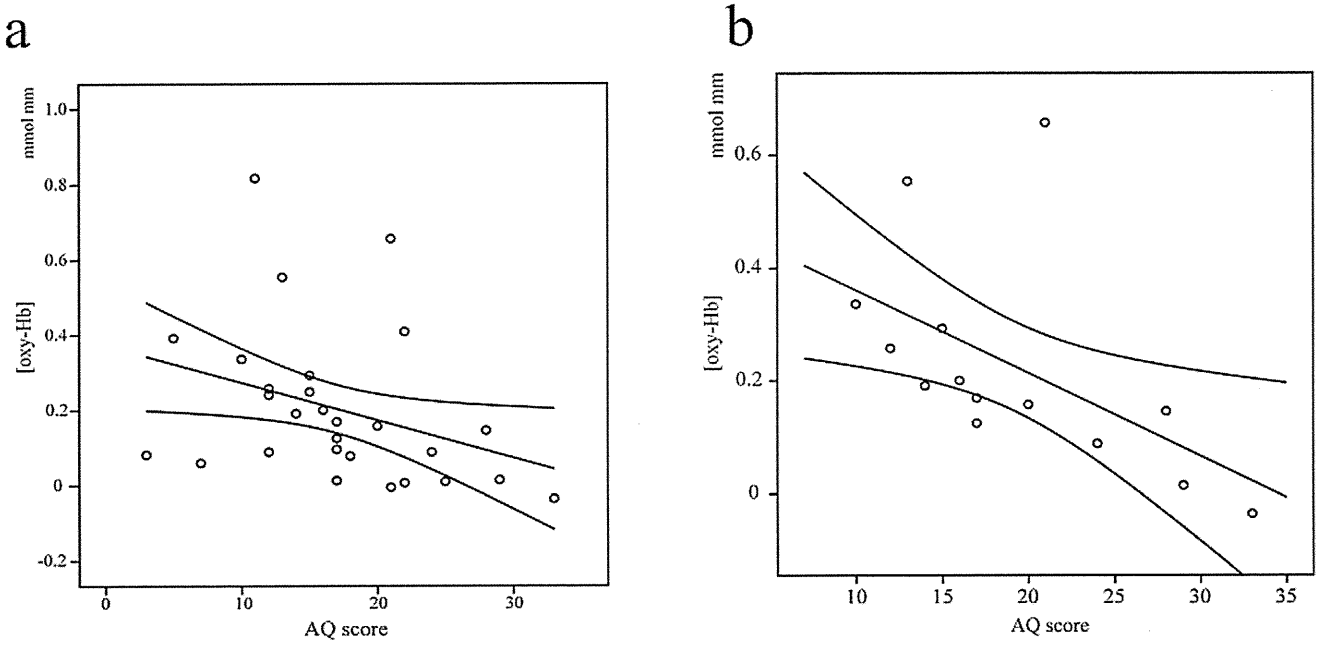

Figure 3. Correlation between autistic traits assessed by the Autism-Spectrum Quotient (AQ) and brain activation. a: Total AQ score vs. the oxygenated haemoglobin concentration ([oxy-Hb]) as measured by near-infrared spectroscopy (NIRS) in the left superior temporal sulcus (STS) among all participants. **b:** Total AQ score in male subjects vs. [oxy-Hb] as measured by NIRS in the left STS.
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Left STS and Autistic Traits

AQ scores were negatively correlated with rCBV increases during face-to-face conversations only in the left STS region; the typically developed (non-ASD) subjects with higher levels of autistic traits demonstrated lesser brain activation, especially in males. Individuals with ASD show considerable variation in the severity and extent to which they exhibit characteristics of the disorder. This heterogeneity has led some researchers to posit that ASD lies on a continuum of social-communication difficulties [17,18] that extends into the 'typical' population [30]. Consistent with this hypothesis, behavioural studies of typical participants have shown effects of the spectrum of autism traits on tasks that are impaired in ASD [19,31,32].

The relationship between the STS and ASD has been examined repeatedly in structural MRI and functional neuroimaging studies performed in the resting state using single-photon emission computed tomography (SPECT) and positron emission tomography (PET). In an MRI study using voxel-based morphometry, Levitt et al. [33] investigated anatomic shifting of the STS in an autistic group compared with a normal group, and Boddaert et al. [34] observed that autism is associated with bilateral anatomical abnormalities localized in the STS. Using SPECT in the resting state, Ohnishi et al. [35] reported decreases in rCBF in the superior temporal and prefrontal cortices in autistic patients compared with controls. Furthermore, von dem Hagen et al. [30] recently identified a relationship between autistic traits in the typical (non-ASD) population and the STS using MRI.

Moreover, fMRI activation studies using several social cognitive stimuli have demonstrated impaired STS function in high-functioning ASD subjects under several conditions: bilaterally in a face perception task [36], a voice perception task [37], and a theory-of-mind task [4], as well as right STS dysfunction in a face perception task [2] and an eye-gaze processing task [38]. Our finding of hypoactivation in the STS in subjects with higher autistic trait scores is consistent with these previous findings.

However, in our study, autistic trait scores correlated with brain activation only in the left STS. We consider that this result may be due to the task characteristics in this study. Because the conversation consisted of speaking, i.e. a language function, effects only in the left STS could be due to hemisphere laterality, although the probes were not located in language regions. However, 2 previous PET studies have also shown left STS dysfunction in ASD. Meresse et al. [39] found a significant negative correlation between rCBF in the left superior temporal gyrus and the Autism Diagnostic Interview-Revised scores of autistic patients in the resting state, suggesting that left superior temporal area hypoperfusion is related to the severity of autistic traits. Boddaert et al. [34] observed left temporal area hypoperfusion in autistic patients by PET during a complex auditory processing task.

Gender and Autistic Traits

In this study, a significant correlation between brain activation and autistic trait scores was only observed in the left STS in male subjects. Gender differences in such a correlation appear reasonable because the prevalence of autism is overwhelmingly higher in males than in females, and the prevalence of autistic traits in healthy populations is higher in males than in females [40], although there was no gender difference in AQ in our subjects. In addition, Baron-Cohen [25] has proposed the 'extreme male brain' theory of autism, which hypothesizes that autism can be considered an extreme of the normal male profile. The gender differences in the correlations between brain activation and autistic traits observed in the present study may support this theory. However, it is important to note that during the face-to-face conversations, the interviewers in this study were all male. The male gender of the interviewer may have had differential effects on brain activation in male and female participants, because, for example, brain activation has been demonstrated to vary according to the gender of the face presented in an fMRI study using a facial perception task [41].

Limitations and Future Directions

There were some methodological limitations in this study. First, the sample size was small, and the participants were all medical students or medical interns. This raises the possibility that the participants were not representative of the general population, because AQ scores differ depending on affiliation, e.g. science students score significantly higher than do humanities students [19]. Most medical students in Japan take science courses; therefore, there may have been sampling effects in this study.

Second, although the task design had some limitations as an exact social cognitive task and was unsatisfactory for reproducing an ordinary social-communication situation, it was sufficient for a preliminary investigation of social cognition in a realistic task setting. To eliminate qualitative and quantitative differences in conversation between participants, we imposed unnatural regulations (such as a conversation cycle of 15 s) and a limited topic of conversation (food). Future studies would benefit from a more sophisticated task design or alternative experimental conditions that limit some social cognitive modules, such as eye-gaze or face perception of the subjects, or that specify features such as specific emotional loading or situational context.

Third, NIRS has some methodological limitations, including low spatial resolution (about 3 cm), and it lacks the ability to assess deep brain structures. We chose the STS as the region of interest corresponding to the 5 Chs shown in Figure S1 (online). This region also includes areas around the lateral upper temporal region, i.e. the superior temporal gyrus, temporal pole, and STS. Thus, there remains the possibility of detecting activation of other parts of the lateral upper temporal region in addition to the STS. Strictly speaking, the pathological substrate of ASD and the brain area responsible for social cognition is considered to be the medial PFC, not the entire PFC. However, it is impossible to distinguish the medial PFC from the other areas of the PFC because of the low spatial resolution of the NIRS technique. Thus, it is reasonable to argue that in the present study, the main functions of the PFC were executive functions, which correspond to the dorsolateral PFC. In the future, when NIRS achieves finer spatial resolution, it will be desirable to distinguish between activation of the medial PFC and the dorsolateral PFC. In addition, the probes in this study covered only the region around the frontal area. Involvement of other cortical areas and deep brain structures could not be determined.

Supporting Information

Figure S1 Near-infrared spectroscopy (NIRS) positioning and diagram of light sources, light detectors, and channels. Upper: The NIRS probe on the head (right) and sensor allocations on a probe (left). Red indicates a near-infrared light source, white indicates a near-infrared light detector, and green indicates an NIRS measurement channel. **Lower:** The locations of the NIRS channels were probabilistically estimated and anatomically labelled in the standard brain space according to Tsuzuki et al. [27]. We identified 4 regions of interest: the right prefrontal cortex (PFC) for the 5 channels located in the right prefrontal lobe, the right superior temporal sulcus (STS) for the 5

channels located in the right temporal lobe, the left PFC for the 5 channels located in the left prefrontal lobe, and the left STS for the 5 channels located in the left temporal lobe.
(TIF)

Table S1 Characteristics of Participants. Characteristics of participants and behavioural data.
(XLSX)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: MS YT MF. Performed the experiments: MS YT YA KN NS. Analyzed the data: MS. Contributed reagents/materials/analysis tools: MS. Wrote the paper: MS MF MM.

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Chapter 7
Electrophysiological Imaging Evaluation of Schizophrenia and Treatment Response

Tomiki Sumiyoshi, Yuko Higuchi, Toru Ito, and Yasuhiro Kawasaki

Abstract Neuroimaging data provide various insights into altered functions and structures in the brain of subjects with schizophrenia. While some blood flow measures, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are in the range of second order. In contrast, electromagnetic recordings, e.g. electroencephalography (EEG) and magnetoencephalography, directly detect neural activity that occurs in the range of milli-second order. In spite of its feasibility, analysis with traditional EEG methods has been associated with the limited ability to localize aberrant signals. However, the recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) and its modified versions (e.g. sLORETA), improves the spatial resolution of EEG at rest and event-related potentials (ERPs), such as P300 and mismatch negativity by providing three-dimensional distribution pattern of these electrophysiological activities. In this chapter, the authors present recent findings from electrical neuroimaging studies of schizophrenia in relation to the neural basis of psychotic symptoms and cognitive deficits of the illness, as well as treatment response. These research areas are likely to facilitate the development of practical and reliable biomarkers to predict symptom severity, improve long-term outcome, and pave a new avenue to early intervention of schizophrenia.

Keywords EEG · Event-related potentials · P300 · MMN · Neuro imaging · LORETA · Cognition · Schizophrenia

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Abbreviations

AAPDs	Atypical antipsychotic drugs
EEG	Electroencephalography
LORETA	Low resolution electromagnetic tomography
MMN	Mismatch negativity

Introduction

There is considerable evidence for associations between social functioning/community outcome and cognitive function, as evaluated by neuropsychological tests, such as the MATRICS Consensus Cognitive Battery in patients with schizophrenia [1]. Therefore, neural substrates underlying impaired cognitive performance need to be elucidated, particularly for the development of novel therapeutic methods for the illness.

While brain imaging methods based on blood flow, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are limited compared to neurophysiological paradigms, e.g. electroencephalography (EEG) and magnetoencephalography. Specifically, electrophysiological biomarkers, such as EEG and event-related potentials (ERPs), have been suggested to provide objective indices of cognitive dysfunction in schizophrenia, and be more sensitive to drug-induced changes compared with other functional imaging modalities [2].

Recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) [3] and its modified versions (e.g. sLORETA) [4], has improved the spatial resolution of ERPs, e.g. P300 and mismatch negativity (MMN), by providing three-dimensional distribution pattern of these electrophysiological activities. This chapter provides recent findings from electrical neuroimaging studies on neural basis for psychopathology of schizophrenia as demonstrated by current source imaging of EEG and ERPs in discrete brain areas, and response to psychotropic drugs in relation to cognition and functional outcome.

LORETA Imaging of EEG in Schizophrenia

Scalp distributions of EEG power of various frequency bands are generally ambiguous [5], and depend on the reference sites used. Therefore, numerical analyses, such as dipole source modeling, are required to obtain precise locations of EEG generators.

LORETA has been developed to provide three-dimensional tomography of brain electrical activity, which only requires simple constraints ("smoothness of the solution"), and predetermined knowledge about the putative number of discernible source regions is not necessary (Fig. 7.1). With this method, brain electrical data

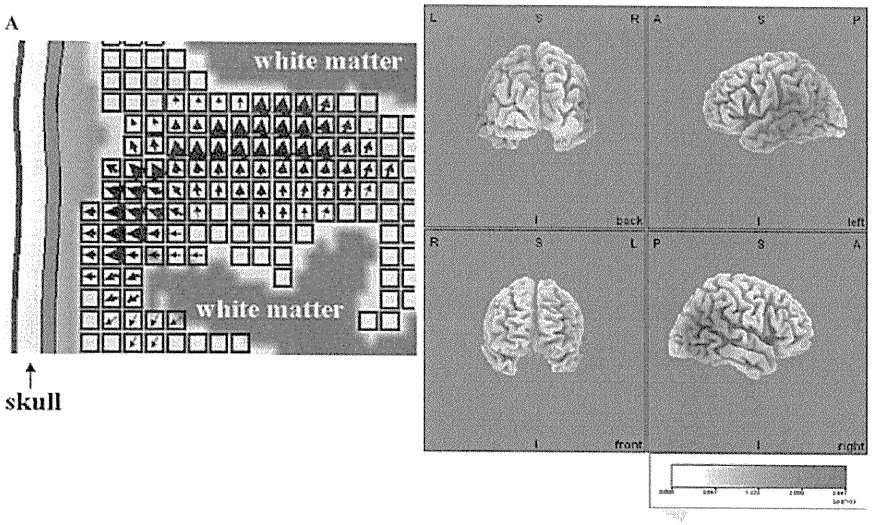

Fig. 7.1 Concept of low resolution electromagnetic tomography (LORETA) developed by Pascual-Marqui [3]. Three-dimensional imaging of LORETA values [mA/mm^2] is derived from 2394 voxels of the whole brain [8]

with high time resolution are transformed into functional imaging of brain activities, since brain electrical activity can be analyzed separately for the different EEG frequency ranges. LORETA has also been widely used for statistical comparisons of intracranial current density distributions between control subjects and patients with neuropsychiatric disorders [6, 7].

Previous investigations [3, 8] suggest that enhanced delta band activity in the prefrontal cortex is associated with the pathophysiology of schizophrenia. Specifically, negative symptoms have been associated with structural impairment in the prefrontal cortex, and have been hypothesized to arise from decreased dopaminergic activity in this brain region [9]. These observations indicate a role for prefrontal cortex in the generation of negative symptoms. With these backgrounds, we sought to determine if some components of EEG, such as delta band activity, would be increased in brain areas relevant to the pathophysiology of schizophrenia, e.g. prefrontal cortex.

As shown in Fig. 7.2 comparisons of current source density, as represented by LORETA values, between patients with schizophrenia and healthy control subjects revealed a significant increase in delta band activity for patients, with a maximum difference found at the left inferior temporal gyrus. A significant increase in delta band activities was also found for the right middle frontal gyrus, right inferior frontal gyrus, right superior frontal gyrus, and right parahippocampal gyrus. These data suggest LORETA analysis of three-dimensional distribution of EEG current density provides a measure of aberrant electrophysiological activity specific to the brain regions responsible for the manifestation of negative symptoms.

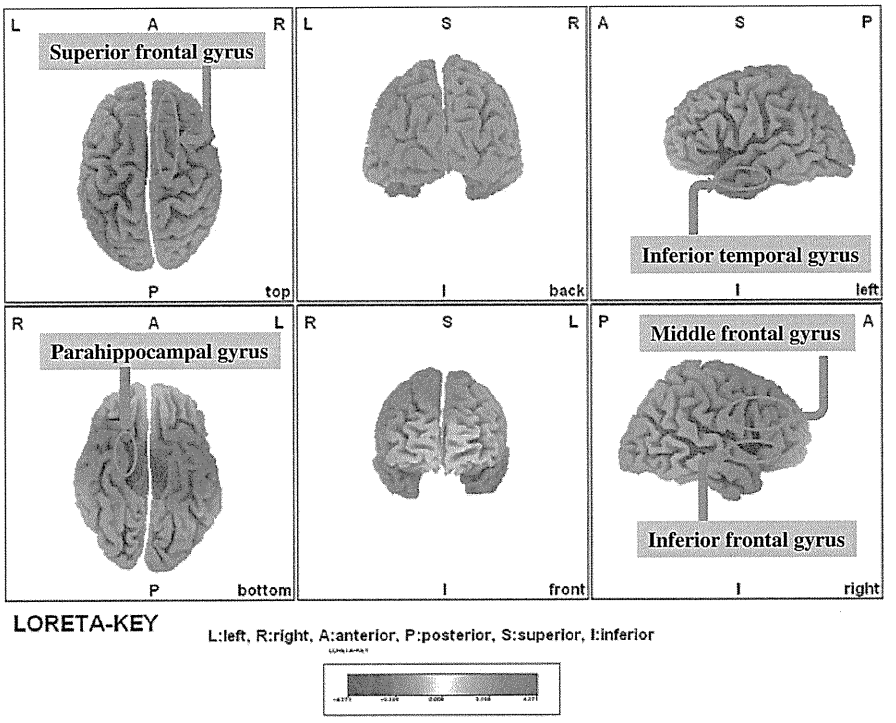

Fig. 7.2 LORETA current source density of *delta* band activity is increased in schizophrenia ($P < 0.001$, Bonferoni correction)

P300 Current Source Imaging and Psychopathology

Reduced amplitude of the P300 component during the auditory oddball task is one of the most consistent findings in patients with schizophrenia [10–12] (Fig. 7.3). However, little information is available about exact relationship between the clinical symptomatology of schizophrenia and the neurophysiological disturbances underlying the P300 abnormality. It is reasonable to assume that anatomically distinct neural substrates responsible for positive or negative symptoms independently contribute to the generation of the P300 component, because this ERP measure is thought to be a composite representation of neural activity in anatomically distinct generators [13–16].

To test this hypothesis, LORETA was used to compute the voxel-wise distribution of brain electrophysiological activity of the P300 component in order to identify brain regions in which the P300 current density is correlated with severity of psychotic symptoms of schizophrenia. Then, we applied the statistical parametric mapping (SPM) methods [17] to LORETA current density images of the P300 component [18, 19].

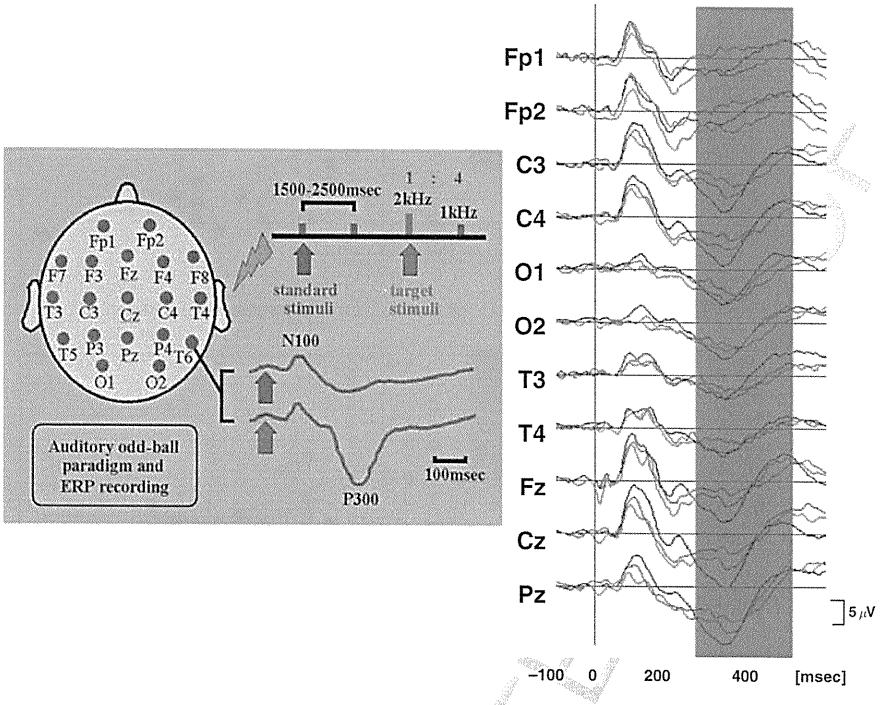

Fig. 7.3 Impaired P300, an event-related potential (ERP), as an endophenotypic marker of schizophrenia. In the right figure, black lines represent data for normal controls, while blue and red lines indicate data for patients before and after treatment with olanzapine, respectively

Results of the SPM one-sample t-test showed that P300 sources are localized in the bilateral medial frontal and medial parietal cortex, bilateral superior temporal gyrus (STG), right temporo-parietal junction, and left lateral prefrontal cortex. With regard to the relationship between the P300 current density and the BPRS Total score, voxel-based whole brain analysis without any hypothesis identified peak voxels of significant negative correlation located at the left STG and right medial frontal region. As shown in Fig. 7.4 (*left*), statistically significant voxels formed clusters within these brain regions. Mean current density values of the cluster in the STG elicited significant relationships with the Positive subscale score Fig. 7.4 (*right*). On the other hand, current density values of the cluster in the medial frontal region revealed a significant relationship with the Negative subscale score.

These findings indicate pathological neural activities of anatomically distinct generators contribute to the generation of the abnormal P300 component [20]. Our data were consistent with the proposal that negative symptoms are associated with neural deficits in the frontal lobe, while those in the temporal lobe are responsible for positive symptoms [21–23]. Taken together, the present results support the concept that the abnormal functional connectivity of fronto-temporal neural network plays a crucial role in the pathophysiology of schizophrenia [24–27].

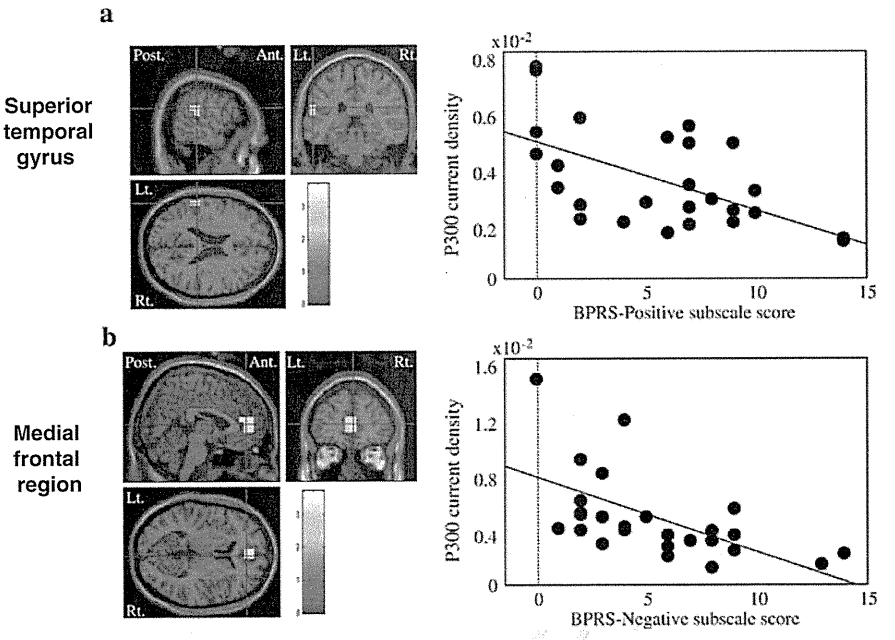

Fig. 7.4 Severity of psychotic symptoms is correlated with P300 current source density in discrete brain regions: A LORETA study [20]

ERPs Activity in Discrete Brain Regions and Effect of Neuroleptic Treatment

P300 amplitudes have been reported to be diminished in patients with schizophrenia, which differs in its effect size topography across the midline and temporal electrode sites [11, 28]. Specifically, Kawasaki et al. [29] found negative correlations between auditory P300 amplitudes and severity of psychotic symptoms of schizophrenia. Renoult et al. [30] report a positive correlation between differences in P300 amplitudes at temporal sites (T4-T3) and severity of positive symptoms and worse global functioning, consistent with the association between low P300 amplitudes and verbal memory deficits in schizophrenia [31, 32]. We reported the first observation that P300 current source density, as evaluated by LORETA, is decreased in several brain regions, especially the STG, precentral gyrus, middle frontal gyrus, and presumes (all in the left side) in patients with schizophrenia as compared with normal controls (Fig. 7.5) [33]. Our findings have been confirmed by an independent group of investigators [34].

Cognitive function, such as verbal memory, attention, and executive function, is a major determinant of outcome in patients with schizophrenia [35, 36]. The second generation antipsychotics, or so-called "atypical antipsychotic drugs (AAPDs)", have been found to partially improve cognitive disturbances of schizophrenia [37]. There is accumulated evidence for the ability of AAPDs, e.g. clozapine, olanzapine, risperidone, quetiapine, melperone, and ziprasidone and perospirone to ameliorate

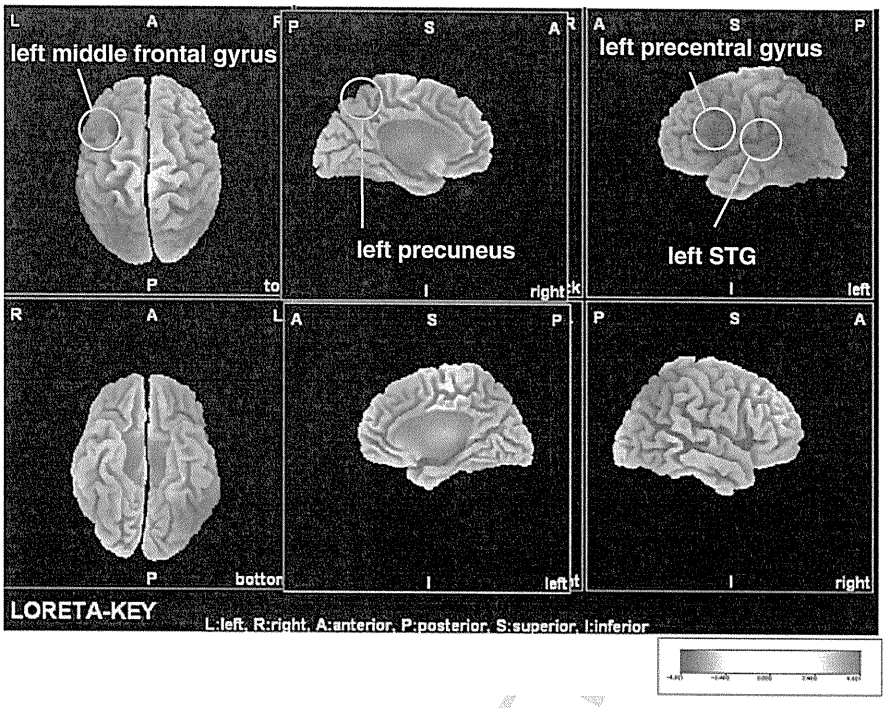

Fig. 7.5 Statistical non-parametric mapping on LORETA images of P300 current density. LORETA values in the marked areas in the left hemisphere were lower for schizophrenia patients compared to control subjects ($P < 0.001$) [33]

cognitive impairments in patients with schizophrenia (reviewed by Sumiyoshi et al. [38]), although their effects have been under scrutiny [39–41]. So far, there is limited information about the neurophysiological mechanisms underlying the ability of neuroleptic treatment to modulate cognitive performance in subjects with schizophrenia.

Umbricht et al. [42] found that treatment with clozapine but not haloperidol increased P300 amplitudes in patients with schizophrenia. Subsequently, Niznikiewicz et al. [43] observed an increase in P300 amplitudes in left temporal electrodes during treatment with clozapine, indicating a region-specific response to pharmacological treatment. We conducted clinical trials [33, 44] to determine if decreased P300 current source density in brain regions responsible for the generation of psychopathology, such as the left STG and prefrontal cortex, is recovered by long-term treatment with olanzapine, and if this change in P300 activity is correlated with improvement of cognitive performance and functional outcome in patients with schizophrenia.

As shown in Fig. 7.6 LORETA images of P300 from patients at baseline elicit lower P300 current density in the left hemisphere compared with normal controls. However, after 6-months treatment with olanzapine, P300 current density in the STG was increased, and the left-dominant laterality pattern of P300 current source

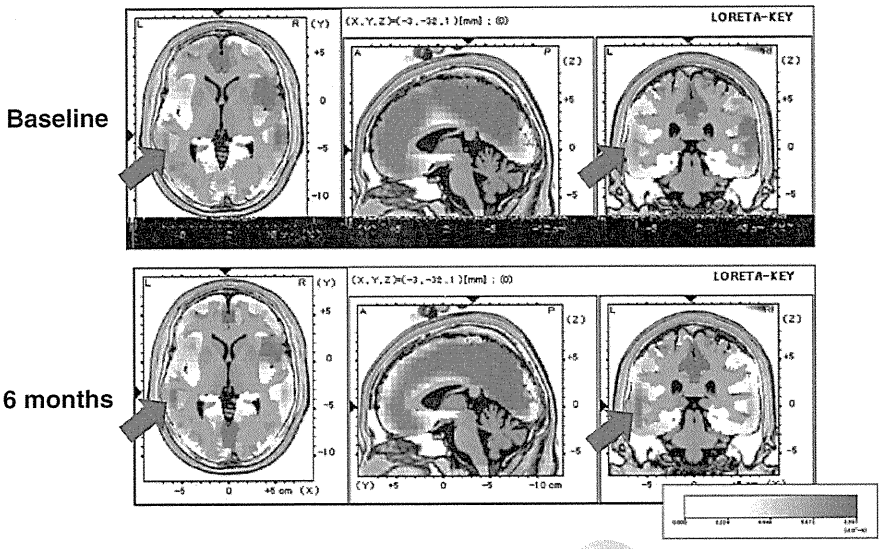

Fig. 7.6 LORETA images of P300; effect of olanzapine treatment. Six-month treatment with olanzapine enhanced P300 current source density in the left STG (indicated by *arrows*) [33]

density was noted, which is similar to the pattern of healthy controls [33, 44]. Moreover, significant correlations were noted between changes of verbal memory performance and LORETA values of the left STG, and between changes of quality of life and LORETA values of the left middle frontal gyrus (Fig. 7.7) [33]. These observations suggest that changes in cortical activity, as measured by EEG, are

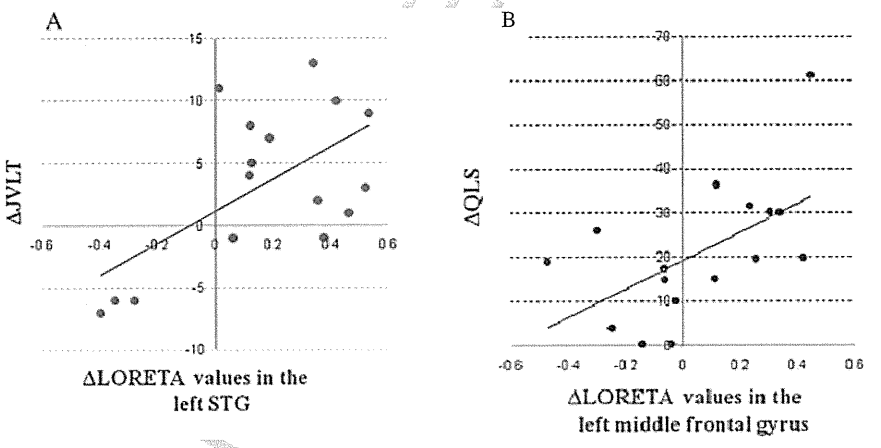

Fig. 7.7 (**A**) Changes in P300 current source density in the left STG by olanzapine were correlated with improvement in verbal memory, as measured by the Japanese Verbal learning Test (JVLT). (**B**) Changes in P300 current source density in the left middle frontal gyrus by olanzapine were correlated with improvement in quality of life, as measured by the Quality of Life Scale (QLS)

responsible for the ability of some antipsychotic drugs to improve cognitive and functional status in patients with schizophrenia.

From the clinical point of view, it is meaningful to examine the effect of type of antipsychotic drugs on the pattern of ERPs activation, as these compounds have been reported to possess differential profiles in terms of binding affinity for various neurotransmitter receptors [45]. Specifically, postmortem studies report that the serotonin-5-HT1A receptor density is increased in prefrontal cortical areas in subjects with schizophrenia [46, 47], suggesting altered 5-HT1A receptor-mediated transmission in this brain region [48, 49]. This concept is in agreement with clinical observations that augmentation therapy with 5-HT1A partial agonists, e.g. buspirone and tandospirone, enhanced the performance on some neuropsychological tests representing frontal lobe function in patients with schizophrenia [38, 50]. Therefore, it is conceivable that neural activity in frontal cortical regions would be enhanced by treatment with antipsychotic drugs with agonist actions at 5-HT1A receptors, such as perospirone [45], in patients with schizophrenia.

Using the same treatment paradigm as in the olanzapine study, above, we investigated the effect of perospirone on P300 current source density, as evaluated by the sLORETA method [4], in patients with schizophrenia, and examine the relationship between changes of P300 activity vs. performance on a cognitive task measuring the ability to evaluate component actions of social situations, which is related to frontal lobe function. As shown in Fig. 7.8 comparison of P300 current source density between baseline and 6-month after the start of treatment revealed a significantly enhanced neural activity in the left superior frontal gyrus, while conventional assessment of P300 amplitudes and latency were not significantly changed [51]. Some of the subjects studied here had been pre-treated with other antipsychotic drugs, including olanzapine, which are devoid of a noticeable affinity for 5-HT1A receptors. Therefore, our observations with perospirone provide further support to the

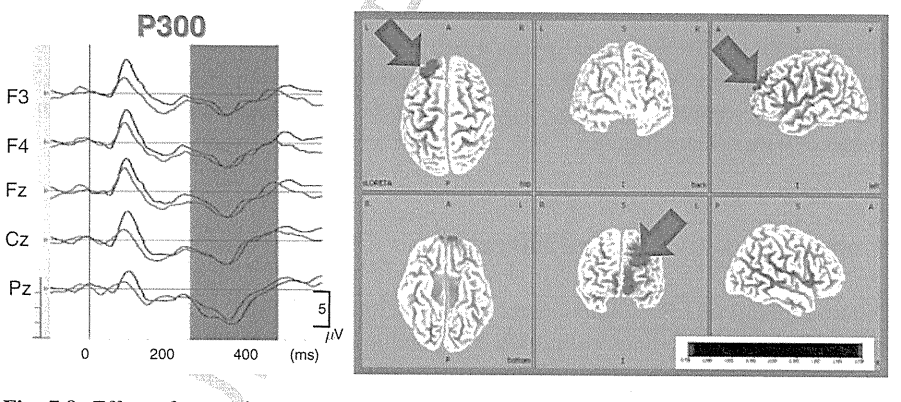

Fig. 7.8 Effect of perospirone on P300 current source density in patients with schizophrenia. Six-month treatment with perospirone enhanced P300 activity in the left superior frontal gyrus (comparison of P300 sLORETA values between before and after 6-month treatment) [51]

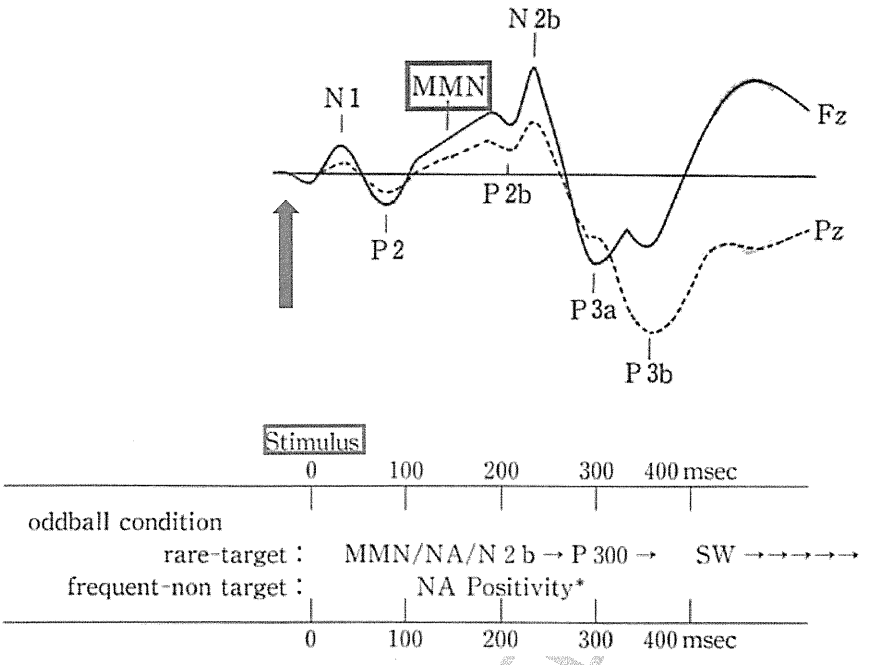

Fig. 7.9 ERP waveforms in response to the odd-ball tasks (rare-target)

concept that stimulation of 5-HT1A receptors may mediate the ability of this agent to increase P300 current source density in the left prefrontal cortex.

Mismatch negativity (MMN) is another component of ERPs generated in response to occasional variations of acoustic stimuli (Fig. 7.9) and is suggested to reflect *pre-attentive* cognitive operations [52]. We recently found the addition of tandospirone, a 5-HT1A partial agonist and anxiolytic [50, 53], was effective for enhancing MMN [54]. This is consistent with previous reports that 5-HT1A agonists, e.g., tandospirone [50, 53, 55], buspirone [38], and perospirone [51, 56], ameliorated cognitive deficits related to frontal and temporal lobe function in subjects with schizophrenia.

Conclusions and Future Directions

Neuroimaging of ERP components, such as P300 and MMN, are also expected to provide an objective diagnostic tool. We conducted discriminant function analysis of multivariate linear model using the statistical parametric mapping (SPM) in order to construct an optimal model to distinguish between healthy controls and patients with chronic schizophrenia [57] (Fig. 7.10). Although the classification power was not enough due, possibly, to the fact that these patients were mixed in terms of