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LORETA Current Source Density for Duration Mismatch Negativity and Neuropsychological Assessment in Early Schizophrenia

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Abstract

Introduction: Patients with schizophrenia elicit cognitive decline from the early phase of the illness. Mismatch negativity (MMN) has been shown to be associated with cognitive function. We investigated the current source density of duration mismatch negativity (dMMN), by using low-resolution brain electromagnetic tomography (LORETA), and neuropsychological performance in subjects with early schizophrenia.

Methods: Data were obtained from 20 patients meeting DSM-IV criteria for schizophrenia or schizophreniform disorder, and 20 healthy control (HC) subjects. An auditory odd-ball paradigm was used to measure dMMN. Neuropsychological performance was evaluated by the brief assessment of cognition in schizophrenia Japanese version (BACS-J).

Results: Patients showed smaller dMMN amplitudes than those in the HC subjects. LORETA current density for dMMN was significantly lower in patients compared to HC subjects, especially in the temporal lobes. dMMN current density in the frontal lobe was positively correlated with working memory performance in patients.

Conclusions: This is the first study to identify brain regions showing smaller dMMN current density in early schizophrenia. Further, poor working memory was associated with decreased dMMN current density in patients. These results are likely to help understand the neural basis for cognitive impairment of schizophrenia.

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Introduction

Schizophrenia is a chronic and progressive psychotic disorder that emerges mainly in late adolescence or early adulthood. Patients with the illness exhibit positive symptoms and negative symptoms, as well as disturbances of various domains of cognitive function, e.g. verbal memory, working memory, executive function, and attention [1,2]. In particular, cognitive impairments have been shown to disturb their social activities, work outcome, and quality of life. Recent studies [3,4] report that mild cognitive deficits already exist before the onset of schizophrenia, or "at risk mental state" (ARMS). The neural substrates for cognitive deficits may include some brain regions, such as hippocampus and parahippocampal gyrus [5–8].

Mismatch negativity (MMN) is one of the event-related potentials (ERPs) generated by a deviant (infrequent) stimulus. MMN is elicited even under pre-attentive conditions, and reflects an automatic pre-attention process. Generation of the MMN is an indicator of auditory sensory memory, and represent information processing dependent on some components of the auditory cortex, e.g. superior temporal gyrus [9–11]. Previous studies using low-resolution brain electromagnetic tomography (LORETA), fMRI, and other procedures have demonstrated that MMN reflects activities of a neural network involving several brain structures. Among them, the auditory cortex plays a key role in the complex neural architecture of sensory discrimination [12–14].

The feature of MMN waveforms varies according to type of deviant stimuli, i.e. frequency, duration, intensity, and location. For example, diminished MMN amplitudes reflect cognitive decline in psychiatric conditions [15]. In schizophrenia, smaller amplitudes of MMN, especially duration MMN (dMMN), have been reported [3,16–19].

Several attempts have been made to relate MMN amplitudes and neuropsychological performance [17–21]. Lin et al. used predictive multivariate logistic regression model, and demonstrated dMMN and performance IQ, evaluated by the Wechsler Adult Intelligence Scale-Third Edition, can distinguish between schizophrenia patients and healthy control (HC) subjects [22].

LORETA provides three-dimensional images of brain electrical activity [23]. There are only a few reports on LORETA analysis of MMN in schizophrenia. Park et al. (2002) [24] observed a significant decrease in the current density for frequency MMN in the left superior temporal gyrus and left inferior parietal gyrus in patients with schizophrenia. Recently, Takahashi et al (2013)

report reduced dMMN current density at right medial frontal gyrus, right cingulate gyrus, and right paracentral lobule in patients with chronic schizophrenia [12]. To our knowledge, there is no report on LORETA analysis of dMMN in early psychosis.

The above considerations indicate the ability of the combination of neuropsychological tests and dMMN to provide an objective measure to diagnose schizophrenia. So far, no study has investigated the correlation between MMN current density in some brain regions, e.g. frontal lobe, and neuropsychological performance.

Therefore, this study was conducted to test the hypotheses that 1) patients with schizophrenia would exhibit decreased dMMN current density in brain areas relevant to the pathophysiology of the illness, such as some temporal lobe structures [25], and 2) reduced dMMN current density in the frontal lobe would be associated with impairment of neuropsychological performance, such as working memory.

Methods

Ethics Statement

This protocol was approved by the Committee on Medical Ethics of the University of Toyama. After a complete and detail description of the study was given, subjects provided written informed consent. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in this research. If the mental status of a subject was impaired to the point where s/he could not understand these issues, the subject was not asked to participate in this research. If there was a possibility that the capacity of a participant to consent was compromised, an additional consent form was obtained from the next of kin, care takers, or guardians of such subjects.

Participants

Subjects were diagnosed by experienced psychiatrists, based on the Structured Clinical Interview for DSM-IV (SCID) for schizophrenia or schizophreniform disorder. Twenty patients (male/female, 9/11; mean [S.D.] age, 27.2 [7.3]) participated in this study. Their duration of illness was less than 2 years. Twenty HC participants (male/female, 14/6; mean [S.D.] age, 25.4 [6.9]) were also recruited. They had no personal history of psychiatric illnesses, including schizophrenia and other psychotic disorders. All participants were right-handed. Psychiatric and treatment histories were obtained from the subjects, family members, and medical records. Subjects with a current history of substance abuse or dependence, seizure, or head injury were excluded from the study. Complete physical examination revealed no neurological illness for all subjects. Demographic data at baseline evaluation are shown in Table 1.

Clinical and neurocognitive assessment

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [26] were administered by an experienced psychiatrist. These data are shown in Table 1.

Neuropsychological performance, measured by the brief assessment of cognition in schizophrenia Japanese version (BACS-J) [27], was evaluated by experienced psychiatrists or psychologists. The BACS-J uses the following assessments in the respective targeted domains; list learning (verbal memory), digit sequencing task (working memory), token motor task (motor function), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function) [27], as shown in Table 1. These scores were transformed into Z-scores using data from healthy volunteers, as previously reported [27,28]. Raters were not informed of subjects' profiles or their diagnoses.

Table 1. Demographic and clinical data.

	Healthy controls (n=20)	Early schizophrenia (n=20)
Male/Female	14/6	9/11
Age (years)	25.4 (6.9)	27.2 (7.3)
	range, 16–45	range, 16–38
Education (years)	15.1 (2.9)	13.2 (2.1) *
Age at onset (years)	-	26.5 (7.1)
Duration of illness (years)	-	0.6 (0.5)
Antipsychotic dose (Risperidone equivalent mg/day)	-	2.1 (2.4)
SAPS	-	16.5 (13.2)
SANS	-	53.9 (25.2)
BACS-J (Z-score)#		
Verbal memory		−1.22 (1.59)
Working memory		−1.16 (1.18)
Motor function		−2.52 (1.07)
Verbal fluency		−1.12 (0.77)
Attention		−1.65 (0.75)
Executive function		−0.40 (1.89)

Values represent means (SD).
SAPS, Scale for the Assessment of Positive Symptoms.
SANS, Scale for the Assessment of Negative Symptoms.
BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese version.
*p<0.05, significantly smaller than healthy controls.
SD unit compared to reported values (ref. [27,28]).
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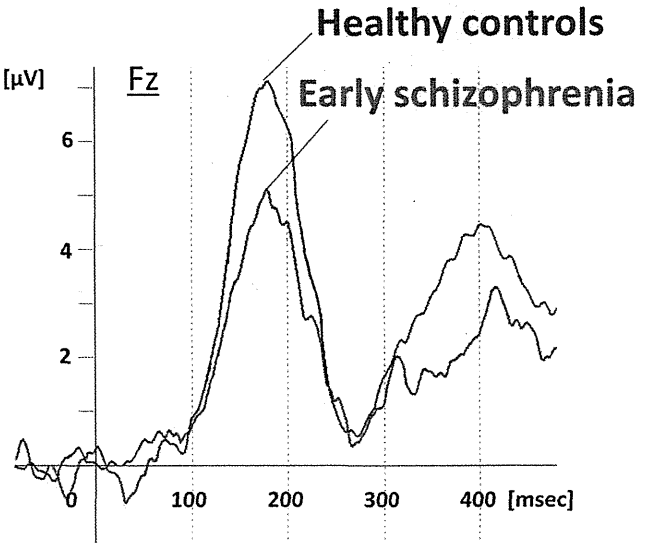

Figure 1. Duration mismatch negativity (dMMN) waveforms at the Fz lead. dMMN waveforms for healthy controls (N=20, blue line) and early schizophrenia (N=20, light green line) are shown.
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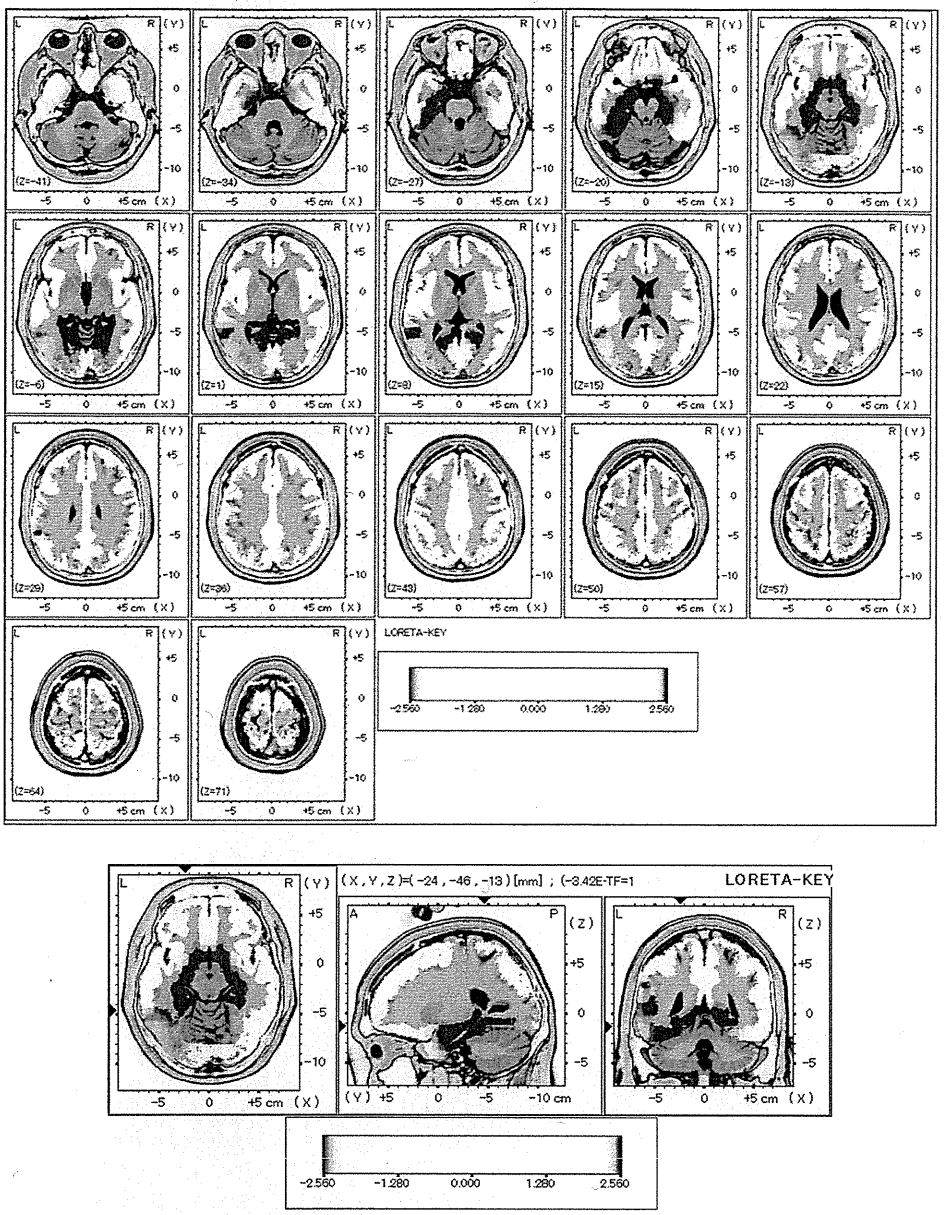

Figure 2. LORETA images for dMMN. Comparison of LORETA current density for dMMN between early schizophrenia (N = 20) and healthy control (N = 20, HC) subjects, as revealed by statistical non-parametric mapping voxel-wise comparison for independent samples. Blue areas represent brain regions showing significantly lower LORETA values for early schizophrenia subjects in comparison with HC subjects.
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Electroencephalographic recording

Electroencephalograms (EEGs) were recorded based on previous reports from our laboratory [29–34]. A 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan), according to the international 10–20 system, was used. Recordings were performed using an electro cap (Electro cap Inc., Eaton, OH) in a sound-attenuated room. Data were collected with a sampling rate of 500 Hz. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth, 0.53–120 Hz, 60 Hz notch filter). Electrode impedance was less than 5 kΩ. Measurements of dMMN were based on our previous report [33]. One thousand auditory stimuli were delivered binaurally through headphones with inter-stimulus intervals of 500 ms. Standard/target tones of 50/100 ms duration were randomly presented with a presentation probability of 0.9/0.1. All tones were 60 dB, 1000 Hz and with a rise-fall time of 10 ms. Subjects were requested to watch a silent animated movie (Tom and Jerry®), and to pay attention to the monitor and ignore the tones. Averaging of ERP waves and related procedures were performed using Vital Tracer and EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan). Epochs were 600 ms, including a 100-ms pre-stimulus baseline. Eye movement artifacts (blinks and eye movements) were manually rejected. MMN waveforms were obtained by subtracting the standard waveforms from the target waveforms. ERP component peaks were identified within the fixed search windows between 100–250 ms. We confirmed the presence of the peaks of MMN in all subjects.

LORETA analysis

LORETA images were obtained by estimating the current source density distribution for epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution applied to the digitized Talairach and Tournoux (1988) [35], based on the established method [23]. LORETA made use of the three-shell spherical head model registered to the Talairach atlas available as a digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al (1993) [36]. The solution space was restricted to cortical gray matter and the hippocampus, as determined by the corresponding digitized Probability Atlas also available from the Brain Imaging Centre. A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% [23]. We used the original LORETA version reported by Pascual-Marqui et al [23]. We calculated LORETA images for each subject in the fixed time frame between the 100–250 ms post-stimulus period to obtain the LORETA value for each voxel. Additionally, we averaged LORETA value containing the following brain regions of interest (ROI): frontal lobe, temporal lobe, parietal lobe, and occipital lobe.

Data analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20 (SPSS Japan Inc., Tokyo, Japan). To investigate differences between groups, dMMN amplitudes at the Fz lead were assessed by independent t-test. Comparisons between early schizophrenia and HC on LORETA source imaging were conducted using voxel-by-voxel unpaired *t*-statistics after logarithmic transformation of the data. Holmes' non-parametric correction for multiple comparisons was applied [37]. Relationships of LORETA current density with BACS-J domain scores, SAPS total scores, and SANS total scores were analyzed using Spearman rank correlations. Bonferroni correction was applied for multiple comparisons. LORETA current density for dMMN did not show a uniformly normal distribution. Therefore, dMMN current density was subjected to natural logarithmic transformation to obtain a more normal distribution. The significance level for all statistical tests was set at $p<0.05$ (two-tailed).

Results

Subjects' profiles

Demographic data of participants are shown in Table 1. The female to male ratio and age were not significant between patients and HC (data not presented). Education level was significantly lower in patients than in HC subjects ($t=2.29$; $p=0.028$).

Neuropsychological assessments

BACS data for patients are shown in Table 1. Except for executive function, the Z-scores of the other domains were below −1.0. Especially motor function was severely impaired.

Comparisons of dMMN amplitudes between HC and early schizophrenia

Figure 1 shows the overall average dMMN waveforms in the Fz lead. dMMN amplitudes in HC and patients (mean ± SD) were 7.9±1.1 μV and 5.6±1.7 μV, respectively. Patients showed significantly smaller dMMN amplitudes than did HC subjects ($t=4.97$; $p<0.01$).

Table 2. Coordinates for brain areas showing the largest differences (top five) between healthy controls and early schizophrenia in dMMN current density.

		(X,Y,Z)	P-value
①	left parahippocampal gyrus	−24, −46, −13	<0.01
②	left fusiform gyrus	−31, −46, −6	<0.01
③	right parahippocampal gyrus	11, −39, 1	<0.05
④	right hippocampus	25, −39, 1	<0.05
⑤	left anterior cingulate	−3, −11, −6	<0.05

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Comparison of LORETA images for dMMN between HC and early schizophrenia

We compared LORETA current source density of dMMN between HC and early schizophrenia. Compared to HC subjects, patients elicited a significantly lower current density in several brain regions, especially those in the temporal lobes, such as parahippocampal gyrus and hippocampus (Figure 2). Additionally, dMMN current density in the frontal structures, such as anterior cingulate, was significantly lower for early schizophrenia. Table 2 demonstrates brain areas showing the largest difference in dMMN current density.

Relationship between psychotic symptoms and LORETA current density for dMMN

There was no significant correlation between the SAPS or SANS score vs. LORETA current density for dMMN in any brain region (data not presented).

Relationship between neuropsychological assessment and dMMN current density

Table 3 demonstrates the relationships between BACS-J domain scores and LORETA current density for dMMN. dMMN current density in the frontal lobe was positively correlated with working memory in patients with early schizophrenia (Table 3,

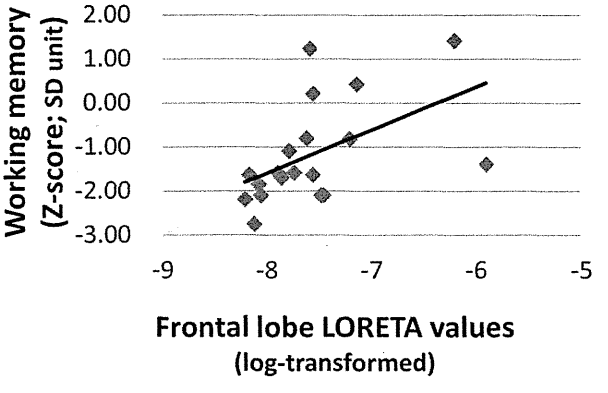

Figure 3. Correlations between dMMN current density and working memory. Scatterplots and least squares regression lines are shown for the correlations between LORETA current density for dMMN (log-transformed) and neuropsychological performance in early schizophrenia.

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Table 3. Spearman correlation coefficients between dMMN current density (log-transformed) in discrete brain regions and BACS-J scores in early schizophrenia.

	verbal memory		working memory		motor function		verbal fluency		attention		executive function	
	r	P	r	P	r	P	r	P	r	P	r	P
Frontal lobe	0.308	0.199	0.587	**0.008**	−0.102	0.678	−0.275	0.254	0.097	0.691	−0.092	0.707
Temporal lobe	0.259	0.285	0.448	0.055	−0.220	0.366.	−0.244	0.314	0.116	0.637	−0.108	0.659
Parietal lobe	0.110	0.655	0.274	0.257	−0.146	0.551	−0.256	0.290	0.150	0.540	−0.221	0.364
Occipital lobe	0.072	0.770	0.336	0.160	−0.100	0.683	0.107	0.663	0.372	0.117	0.028	0.909

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Figure 3). The correlation remained significant even after Bonferroni correction was applied. There were no such correlations for temporal, parietal, and occipital lobes.

Discussion

To our knowledge, this is the first study to report three-dimensional distribution patterns of dMMN current density and neuropsychological performance in early schizophrenia in comparison with healthy controls. LORETA images demonstrated a decreased dMMN current density in brain areas known to be associated with the pathophysiology of the illness, e.g. parahippocampal gyrus, hippocampus, fusiform gyrus, and anterior cingulate [5,6,38,39]. We also observed positive correlations between dMMN current density in the frontal lobe and working memory performance in patients with early schizophrenia.

Reductions in the volume of several brain regions, including frontal cortex and temporal cortex, in schizophrenia subjects and individuals vulnerable to developing the illness have been reported [40–42]. Reduced dMMN current density in the temporal lobe of patients, observed in this study, is consistent with these morphological findings. Specifically, MMN has been considered to be generated by neural activities in the superior temporal cortex and frontal cortex [9–11]. The present data from a more feasible and non-invasive methodology (i.e. EEG) add support to these lines of evidence for the potential role of several discrete brain regions in the pathophysiology of schizophrenia.

Takahashi et al. (2013) report schizophrenia patients demonstrated a smaller dMMN current density in the right medial frontal gyrus [12]. Compared with our data, their results indicate more frontal regions are affected in patients [12]. The discrepancy may be due to the difference in duration of illness. The subjects of Takahashi's study were chronic schizophrenia, with a mean duration of illness of 23.6 years, while that of our subjects was shorter, i.e. less than 2 years. It is possible that the electrophysiological impairment, e.g. dMMN, becomes more extensive as psychosis progresses. In this context, further study is needed to examine a longitudinal course of dMMN in schizophrenia.

Correlations between MMN amplitudes and neuropsychological performance have been an issue for intensive investigations. Several [17–21], but not all [3,22] studies found MMN amplitudes to be related to cognitive function. The present study revealed, for the first time, that dMMN current density in early schizophrenia was correlated with working memory. Perlstein et al. [43] report that this cognitive domain was associated with dorsolateral prefrontal cortex function, as measured by fMRI, consistent with our electrophysiological findings. Further study should clarify sub-region(s) of the frontal cortex whose dMMN current density is specifically associated with working memory.

The limitations of the present study should be noted. Patients with early schizophrenia were taking antipsychotic drugs which are agonists at dopamine receptors, although modulations of dopaminergic transmission have been shown to exert little effect on dMMN [44,45]. Another limitation may be the use of the original version of LORETA. Further study is warranted to examine dMMN in drug-naïve subjects using an updated version of LORETA (e.g. eLORETA, sLORETA), which would be more advantageous for sub-region analyses and/or multiple comparisons.

In conclusion, this study provides, for the first time, information on the brain regions responsible for diminished dMMN amplitudes in subjects with early schizophrenia. Further, we have found associations between poor working memory and decreased dMMN current density in these patients. These results are likely to help understand the neural basis for cognitive impairment of schizophrenia.

Author Contributions

Conceived and designed the experiments: TM T. Sumiyoshi YH. Performed the experiments: TM YH T. Seo. Analyzed the data: TM T. Sumiyoshi YH. Contributed reagents/materials/analysis tools: TM T. Sumiyoshi YH T. Seo MS. Wrote the paper: TM T. Sumiyoshi YH.

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Regular Article

Increased pituitary volume in subjects at risk for psychosis and patients with first-episode schizophrenia

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Aim: Enlarged pituitary gland has been reported in schizophrenia, possibly reflecting hypothalamic–pituitary–adrenal hyperactivity. The aim of the present study was to examine whether individuals at risk of psychosis also have similar changes.

Methods: Magnetic resonance imaging was used to examine the pituitary volume in 22 individuals with at-risk mental state (ARMS; 11 male, 11 female), 64 first-episode patients with schizophrenia (FESz; 37 male, 27 female), and 86 healthy controls. The control subjects were divided into age- and gender-matched controls for ARMS (11 male, 11 female) and FESz (37 male, 27 female).

Results: Both the ARMS and FESz groups had a larger pituitary volume compared with matched controls, but no difference was found between the ARMS and FESz subjects. There was no association between the pituitary volume and clinical variables (symptom measures at scanning, daily dosage or duration of antipsychotic medication) in either clinical group. The pituitary volume did not differ significantly between the ARMS individuals who later developed schizophrenia ($n = 5$) and those who did not ($n = 17$). The pituitary volume was larger in women than in men for all diagnostic groups.

Conclusion: The finding of increased pituitary volume in both ARMS and FESz subjects may reflect a common vulnerability to stress in early psychosis. Further work in a larger ARMS sample is required to examine the possible relationship between pituitary volume and emergence of psychosis.

Key words: at-risk mental state, hypothalamic–pituitary–adrenal axis, magnetic resonance imaging, pituitary gland, schizophrenia.

HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) axis hyperactivity is thought to reflect stress-related hormonal dysregulation and has been described in schizophrenia.[1,2] Although not consistently replicated,[3] previous magnetic resonance imaging (MRI) studies have generally demonstrated enlarged pituitary volume[4–6] with ongoing expansion[7,8] early in the course of schizophrenia, presumably reflecting activation of the hormonal stress response. The patients may also exhibit pituitary atrophy during later courses,[9–11] possibly as a result of prolonged HPA activation.[12] Interestingly, recent neuroendocrine findings in clinical subjects at high risk for developing psychosis (i.e. at-risk mental state; ARMS[13]), such as the association of cortisol level with prodromal or psychotic symptoms[14–17] as well as with

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progression to psychosis,[18] suggest that HPA axis dysfunction may pre-date the onset of psychosis in at least some individuals.[19]

In contrast to these hormonal investigations, there have been only a few MRI studies addressing pituitary volume changes prior to psychosis onset and the results have been inconsistent. In the first MRI study of the pituitary gland in clinical high-risk subjects, Garner *et al.* found no significant volume difference between the ARMS subjects (as a whole or those who later developed psychosis) and controls, but pituitary enlargement was associated with later transition to psychosis (predominantly affective psychosis).[4] They also examined the possible relationship of the pituitary volume to anxiety/depressive or psychotic symptoms, but found no significant results. Thompson *et al.* showed that pituitary volume in ARMS did not correlate with the experience of stressful events, plasma cortisol level, or clinical symptoms, but that study lacked a healthy comparison group.[17] A recent study by Büschlen *et al.* did not replicate a significant difference in the pituitary volume between ARMS with and without transition,[4] but their data (controls < ARMS without later transition < ARMS with transition and first-episode psychosis)[20] were in line with hypothesized pituitary enlargement with the emergence of psychosis. Thus, it remains unclear from the current evidence whether these high-risk subjects have significant pituitary volume changes as compared with controls and whether their pituitary volume is related to clinical characteristics.

The present MRI study investigated the pituitary volume in subjects with ARMS and first-episode schizophrenia (FESz) compared with age- and gender-matched healthy controls. On the basis of previous MRI and neuroendocrine findings suggesting HPA hyperactivity prior to the onset of overt psychosis,[19] we predicted that both ARMS and FESz subjects would have increased pituitary volume compared with matched controls. We also explored the relationship between the pituitary volume and clinical characteristics (e.g. symptom severity, later transition into psychosis, and antipsychotic medication) in these participants.

METHODS

Participants

Twenty-two ARMS subjects were recruited from the Consultation Support Service in Toyama (CAST), which was launched in 2006 as a specialized clinical setting to study and treat young people (aged 15–30 years) at risk for developing psychosis.[21] The ARMS subjects, who had no previous episode of overt psychosis and no clear diagnosis of major depression or borderline personality disorder, were diagnosed according to the Comprehensive Assessment of At Risk Mental States (CAARMS);[13] inclusion into the study required one or more of (i) attenuated psychotic symptoms defined by subthreshold intensity or frequency ($n = 21$); (ii) brief limited intermittent psychotic symptoms with spontaneous resolution ($n = 2$); and/or (iii) family history of psychosis or a personal history of schizotypal personality disorder accompanied by a decline in general functioning ($n = 1$). At intake, they were also assessed using the Beck Depression Inventory (BDI) and State Trait Anxiety Inventory (STAI) (Table 1).[23,24] Eighteen ARMS subjects were antipsychotic naïve at the time of scanning, but three subjects were receiving low doses of atypical antipsychotics (risperidone, blonanserin, or aripiprazole) and one was treated with sulpiride. They were also receiving benzodiazepines ($n = 3$), antidepressants ($n = 1$), and/or tandospirone ($n = 3$). The mental condition of each subject was regularly assessed by experienced psychiatrists to check for the emergence of full-blown psychosis at outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital; five (22.7%) of the ARMS subjects in this group developed schizophrenia fulfilling ICD-10 research criteria[25] and 17 (77.3%) did not develop psychosis during follow up (mean clinical follow-up period after scanning, 15.6 ± 17.4 months).

Sixty-four FESz patients who fulfilled the ICD-10 research criteria,[25] with illness duration ≤1 year ($n = 48$) or under first psychiatric hospitalization ($n = 16$) at the time of scanning,[26–29] were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital (Table 1). The diagnosis of schizophrenia was confirmed for all patients at least 6 months after illness onset based on information obtained from a detailed chart review as well as their clinical symptoms rated at the time of scanning. They were also screened for other neuropsychiatric conditions (e.g. depressive/manic symptoms) by experienced psychiatrists. All but two of the patients were on antipsychotic medication; 18 were treated with typical antipsychotics, 43 were receiving atypical antipsychotics and one received both typical and atypical antipsychotics.

Table 1. ARMS and FESz subject data vs matched controls (mean ± SD)

Parameters	ARMS (11 M, 11 F)	Controls (11 M, 11 F)	Group comparisons
Age (years)	19.1 ± 4.1	19.4 ± 4.2	$F(1,42) = 0.05$, $P = 0.830$
Height (cm)	162.2 ± 9.5	164.3 ± 8.5	$F(1,42) = 0.62$, $P = 0.436$
Education (years)	11.1 ± 1.6	13.1 ± 2.6	$F(1,42) = 8.99$, $P = 0.005$
Parental education (years)	13.8 ± 1.7	12.4 ± 1.6	$F(1,42) = 7.68$, $P = 0.008$
Medication dose (HPD equiv., mg/day)†	2.2 ± 3.1 ($n = 4$)	–	–
Duration of medication (months)	2.3 ± 4.1 ($n = 4$)	–	–
Time between intake and scan (days)	50.8 ± 74.4	–	–
Time between scan and onset (months)	8.2 ± 9.9 ($n = 5$)	–	–
STAI trait at intake‡	65.3 ± 10.9	–	–
STAI state at intake‡	58.4 ± 11.3	–	–
BDI at intake‡	24.1 ± 10.0	–	–
SAPS total at scanning	20.4 ± 10.9	–	–
SANS total at scanning	48.5 ± 19.4	–	–
	FESz (37 M, 27 F)	Controls (37 M, 27 F)	Group comparisons
Age (years)	24.0 ± 4.7	25.1 ± 5.0	$F(1,126) = 1.64$, $P = 0.203$
Height (cm)	164.9 ± 7.6	167.0 ± 7.5	$F(1,126) = 2.60$, $P = 0.109$
Education (years)	13.5 ± 1.9	16.5 ± 2.6	$F(1,126) = 57.55$, $P < 0.001$
Parental education (years)	13.0 ± 2.0	13.2 ± 2.5	$F(1,124) = 0.50$, $P = 0.482$
Onset age (years)	23.1 ± 4.7	–	–
Illness duration (months)	11.2 ± 12.2	–	–
Medication dose (HPD equiv., mg/day)	10.3 ± 8.8	–	–
Duration of medication (months)	8.3 ± 12.6	–	–
SAPS total at scanning	27.3 ± 21.9	–	–
SANS total at scanning	53.1 ± 25.2	–	–

†Different typical and atypical antipsychotic dosages are converted into HPD equivalents using the guideline by Toru.[22]
‡Data missing for one participant. ARMS, at-risk mental state; BDI, Beck Depression Inventory; FESz, first-episode schizophrenia; HPD, haloperidol; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; STAI, State Trait Anxiety Inventory.

The control subjects consisted of 86 healthy volunteers recruited from the community, hospital staff, and university students. Given the sexual dimorphism (male < female) and age-related atrophy of the pituitary gland,[30–32] the control subjects comprised two groups that were age- and gender-matched for ARMS ($n = 22$) and for FESz ($n = 64$), respectively (Table 1). Although the controls did not receive a full diagnostic interview, they were given a questionnaire consisting of 15 items concerning their personal (13 items; e.g. a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric diseases, impaired thyroid function, hypertension, diabetes, and substance use) and family (two items) histories of illness.[33] They did not have any personal or family history of psychiatric illness among their first-degree relatives.

All subjects in this study (ARMS, FESz, and controls) were screened using the same exclusion criteria (except family history of psychiatric illness, which was applied only to controls). They were right-handed and physically healthy at the time of the study, and none had a history of serious head trauma, severe obstetric complications, neurological illness, substance abuse disorder, or serious medical disease (e.g. impaired thyroid function, hypertension, and diabetes). The FESz and ARMS participants were screened for these conditions using a detailed chart review at scanning (FESz) or direct interview at study intake (ARMS). None of the participants was pregnant or taking exogenous estrogens at the time of the study, but hormone levels as well as menstrual cycle in female subjects were not assessed in this study. All participants were

Table 2. Intracranial and pituitary volume (mean ± SD)

Variables	ARMS (11 M, 11 F)	Controls for ARMS (11 M, 11 F)	FESz (37 M, 27 F)	Controls for FESz (37 M, 27 F)
Intracranial volume (cm^3)	1460 ± 132	1500 ± 146	1500 ± 147	1502 ± 150
Pituitary volume (mm^3)	763 ± 124†	697 ± 143	802 ± 153†	708 ± 140

†Significantly larger than age- and gender-matched controls. Statistical analysis for the pituitary gland was based on relative volume. Analysis of covariance with age as a covariate and with diagnosis as a between-subject factor was used for the intracranial volume. ARMS, at risk mental state; FESz, first-episode schizophrenia.

also screened for gross brain abnormalities by neuroradiologists.

The clinical symptoms of the ARMS and FESz subjects were rated at the time of scanning using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS/SAPS).[34] Of the 172 participants in this study, 60 controls (35 male) and 37 schizophrenia patients (21 male) were also included in our previous pituitary study.[35] This study was approved by the Committee on Medical Ethics of Toyama University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

Magnetic resonance imaging procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Erlangen, Germany) with a 3-D gradient-echo sequence fast low-angle shots (FLASH) yielding 160–180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time, 24 ms; echo time, 5 ms; flip angle, 40°; field of view, 256 mm; and matrix size, 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

To assess the pituitary volume, the images were processed on a Linux PC (Fujitsu, Tokyo, Japan) using Dr. View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions to standardize for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images of 1-mm thickness perpendicular to the anterior commissure–posterior commissure line. The signal intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to semi-automatically segment the voxels into brain tissue components and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as described previously;[36] there were no significant group differences for ICV (ARMS vs their controls, $F(1,41) = 0.88$, $P = 0.353$; FES vs their controls, $F(1,125) < 0.01$, $P = 0.984$; and FES vs ARMS vs all controls, $F(2,168) = 0.43$, $P = 0.654$; Table 2).

Pituitary measurements

The pituitary gland volume was manually traced on consecutive 1-mm coronal slices based on a method used by Garner *et al.*[4] Briefly, we traced around the usually well-defined borders of the anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. As presented in Figure 1, the pituitary stalk was excluded from the tracings, but we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect the vasopressin concentration). All measurements were carried out by a trained rater (TT) without knowledge of the subjects' identities or the times of their scans. To determine the reliability of the measurement, a second rater (VL) measured the pituitary volume in a subset of 10 randomly selected brains. Each pituitary volume in these 10 brains was then remeasured after at least 4 weeks by the first rater. Inter- (TT and VL) and intra-rater intraclass correlation coefficients were >0.93.

Statistical analysis

The relative volume of the pituitary gland ([absolute volume/ICV) × 100]) was analyzed using analysis of

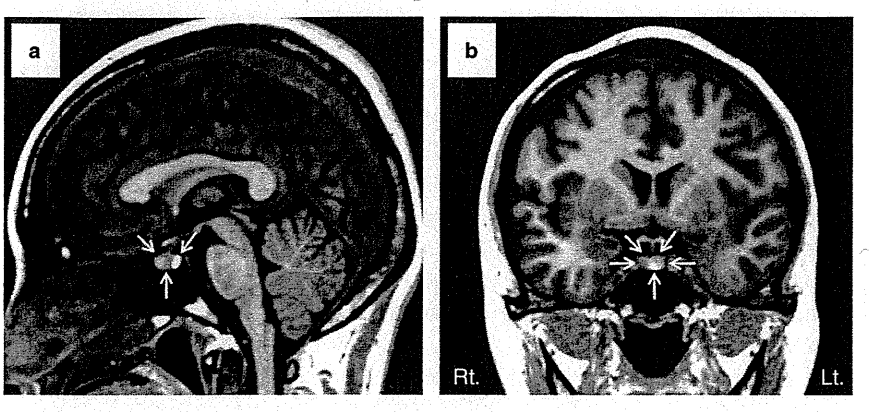

Figure 1. (a) Sagittal and (b) coronal views of the pituitary gland manually traced in this study. The pituitary stalk was excluded from the tracings, but a posterior bright spot was included.

covariance (ANCOVA) with age as a covariate and with diagnosis and gender as between-subject factors. The effect of medication type (typical vs atypical for FESz) and outcome (with vs without later transition for ARMS) on relative pituitary volume was also examined on ANCOVA. Post-hoc Scheffé's tests were carried out to follow up any significant main effects or interactions. Spearman's rank correlations were calculated to examine relationships between relative pituitary volume and the clinical variables. Statistical significance was defined as $P < 0.05$ (two-tailed).

RESULTS

Group comparisons of the pituitary volume

ANCOVAs of the pituitary volume showed significant main effects for diagnosis (ARMS vs their controls, $F(1,39) = 4.94$, $P = 0.032$; FESz vs their controls, $F(1,123) = 15.58$, $P < 0.001$) and gender (ARMS vs their controls, $F(1,39) = 26.39$, $P < 0.001$; FESz vs their controls, $F(1,123) = 113.58$, $P < 0.001$) but not diagnosis × gender interaction (ARMS vs their controls, $F(1,39) = 0.91$, $P = 0.346$; FESz vs their controls, $F(1,123) = 0.66$, $P = 0.417$). Post-hoc analyses showed that both the ARMS ($P = 0.030$) and FESz ($P < 0.001$) groups had a larger pituitary volume compared with matched controls, and female subjects had a larger volume than male subjects ($P < 0.001$; Table 2; Fig. 2). Direct comparison of the pituitary volume between ARMS and FESz showed no significant group difference ($F(1,81) = 1.58$, $P = 0.213$).

These results remained essentially the same even when we added medication dose and duration as covariates, and there was no difference in the pituitary volume between the FESz patients treated with typical ($n = 18$) and atypical ($n = 43$) antipsychotics

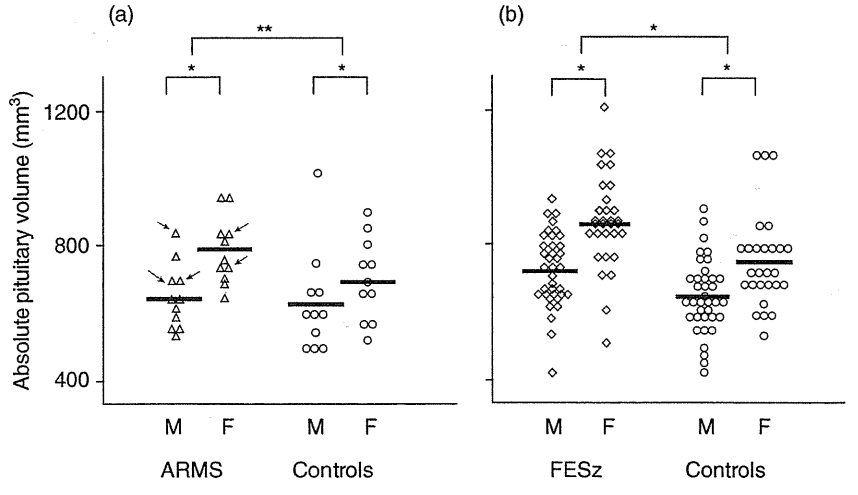

Figure 2. Absolute pituitary volume in the at-risk mental state (ARMS) individuals, controls for ARMS, first-episode schizophrenia (FESz) patients, and controls for FESz. Arrows, ARMS individuals with later transition into psychosis. Horizontal lines, mean. Post-hoc test: $*P < 0.01$, $**P = 0.03$ (statistical analysis for the pituitary gland was based on relative volume).

($F(1,58) = 0.30$, $P = 0.586$). Although the ARMS subjects who were taking antipsychotics at scanning ($n = 4$; pituitary volume, 843 ± 128 mm^3) had a larger pituitary volume than antipsychotic-naïve ARMS subjects ($n = 18$; pituitary volume, 746 ± 120 mm^3), the difference was not statistically significant ($F(1,19) = 1.73$, $P = 0.204$). The comparison of the pituitary volume between the antipsychotic-naïve ARMS and FESz subjects showed no significant group difference ($F(1,77) = 1.60$, $P = 0.209$). When we examined only antipsychotic-naïve ARMS subjects ($n = 18$) and 18 age- and gender-matched controls, pituitary expansion did not reach significance ($F(1,31) = 3.48$, $P = 0.072$). The pituitary volume did not differ significantly between the ARMS subjects who later developed schizophrenia ($n = 5$; pituitary volume, 803 ± 78 mm^3) and those who did not ($n = 17$; pituitary volume, 752 ± 134 mm^3; $F(1,19) = 0.87$, $P = 0.362$).

Correlation analysis

The relative pituitary volume did not correlate with age, education, or parental education in all groups. No significant correlation was found between the pituitary volume and the BDI or STAI (state, trait) score in the ARMS subjects. In the FESz group, the pituitary volume was not significantly correlated with onset age or illness duration. In both the ARMS and FESz groups, no significant correlation was found between the pituitary volume and the total scores for the SANS/SAPS or medication (daily dose at scanning, duration of antipsychotic treatment).

DISCUSSION

This MRI study identified an enlarged pituitary volume in both subjects with ARMS and patients with FESz compared with healthy controls. The effect of medication is an important consideration for pituitary findings,[7,9,10,37] but we found no significant effect of daily dose or duration of antipsychotic treatment on the pituitary volume. Consistent with previous reports,[4,17] the pituitary volume did not correlate with clinical symptoms in either clinical group. Despite the relatively small number of subjects with ARMS, the present findings suggest that these high-risk subjects may share HPA hyperactivity with FESz patients as a possible indicator of common stress vulnerability.

Pituitary volume in early psychosis

The present finding of enlarged pituitary volume in FESz is consistent with previous MRI studies,[5,6,8,20] supporting the role of HPA hyperactivity in the development of psychosis.[2,18] To our knowledge, however, there have been only two MRI studies of the pituitary volume in ARMS as compared with healthy controls, which have yielded partly inconsistent results. Garner *et al.* found no significant group difference in the pituitary volume between the ARMS and controls, but the ARMS subjects who later developed psychosis (ARMS-T) had a larger pituitary volume than those who did not (ARMS-NT).[4] The present results were similar to those of Büschlen *et al.*, who reported that the pituitary volume increased in the order of healthy controls to ARMS-NT to ARMS-T and first-episode psychosis, although the difference between the ARMS-T and -NT was not statistically significant.[20] As discussed by Büschlen *et al.*,[20] these inconsistencies may be partly due to different ascertainment strategies, as well as different characteristics, of regional psychiatric services. In fact, Garner *et al.*, who included ARMS subjects with a comorbid diagnosis of major depression or borderline personality disorder, suggested the role of the pituitary volume as a predictor of psychotic major depression,[4] whereas the ARMS-T subjects in the present study and those of Büschlen *et al.*,[20] neither of whom included ARMS subjects with those comorbidities, predominantly developed schizophrenic psychosis. Nevertheless, these MRI studies generally imply that these clinical high-risk subjects could exhibit pituitary expansion at least in some individuals, supporting the notion that an enhanced HPA axis response to stress appears to be part of the biological vulnerability to psychosis.[19] This notion may also be supported by hormone[38–40] and neuroimaging[35] findings in subjects with schizotypal personality disorder (SPD) who have a higher incidence of developing psychosis than the general population,[41] suggesting that distress related to social deficits or incipient psychotic experience could activate the stress response even without florid psychosis.

Possible underlying mechanism of the pituitary expansion

The present structural MRI study could not address the mechanism for pituitary volume changes, but a recent study by Habets *et al.* showed that higher pitu-

itary volume was associated with increased emotional stress reactivity especially in patients with psychotic disorder.[42] It may be possible that pituitary expansion in the present study reflects HPA axis hyperactivity and a subsequent increase in the size and number of corticotrophs (cells producing adrenocorticotropic hormone; ACTH), which can be explained by an activation of the hormonal stress response.[5,6] Estrogen treatment, hypothalamic tumor, pregnancy, and primary hypothyroidism also lead to pituitary expansion,[43,44] but these common causes of pituitary enlargement were excluded in the present subjects.

Antipsychotic medication could also influence HPA activation,[2,45,46] but the effect of medication on the pituitary volume remains controversial. Recent MRI studies suggested that atypical antipsychotics might reduce pituitary volume in the course of psychosis,[9,10,37] consistent with the notion that antipsychotic medication generally dampens HPA activity in schizophrenia.[1,2,46] In contrast, some antipsychotics may increase pituitary volume, possibly by activating prolactin-secreting cells.[5,7,47] Although we did not find a direct relation between the pituitary volume and medication (daily dose at scanning, duration of antipsychotic treatment), almost all of the present FESz patients had been taking antipsychotics for a substantial period at the time of scanning (mean, 8.3 months) and significant pituitary expansion of the ARMS subjects diminished when we investigated only antipsychotic-naïve ARMS subjects. Thus, the possibility still exists that the pituitary expansion in the present study was partly related to the effect of antipsychotic medication, which should be further examined.

Pituitary volume and clinical characteristics

In contrast to neuroendocrine observations demonstrating the association of plasma or salivary cortisol levels with prodromal (including depressive and anxiety) or psychotic symptoms in ARMS subjects,[14–17] this and previous MRI studies in ARMS found no significant correlation between the pituitary volume and global psychopathology, general functioning, or psychotic symptomatology.[4,17] Direct comparison of plasma and MRI findings in ARMS also showed that pituitary volume did not correlate with either plasma cortisol level or number of glucocorticoid receptors.[17] Our previous study, however, identified a significant relationship between ongoing pituitary expansion and treatment response or severity of positive psychotic symptoms in FESz,[8] suggesting that it is longitudinal pituitary changes during early phases of the illness that are relevant to clinical manifestations of psychosis. Interestingly, a recent study of cortisol level emphasized the role of longitudinal HPA changes in the development of psychosis.[18] Thus, further study of the association of longitudinal pituitary volume changes with HPA functioning and clinical characteristics (e.g. symptom severity, later transition into psychosis) is required to examine the potential role of HPA activity in the emergence of psychosis in vulnerable individuals.

Methodological considerations

A few possible methodological considerations in this study should be taken into account. First, the sample size of the present ARMS group (especially those who later developed psychosis) was relatively small and the clinical follow-up period was short for some individuals. Although we found no significant difference in pituitary volume between the ARMS subjects with and without later transition to psychosis, whether the baseline pituitary volume could predict onset of psychosis should be tested in a larger, well-defined high-risk cohort. Second, although the present findings of pituitary enlargement in early psychosis are thought to reflect state-related HPA axis dysregulation, we did not directly assess pituitary function. The pituitary gland is also considered to be sensitive to prolactin-elevating antipsychotics[7,47] and a recent study reported hyperprolactinemia in antipsychotic-naïve ARMS subjects.[48] The present findings replicated the sexual dimorphism of the pituitary gland volume (female > male),[32] potentially reflecting different endogenous estrogen levels.[49] We did not, however, assess prolactin or estrogen level in this study. Thus, additional assessment of both pituitary volume and hormone levels (e.g. cortisol, ACTH, prolactin, and estrogen) is required. The present study might be also limited by a lack of urine toxicology screening for substance use. Finally, given that HPA axis functioning also appears to be affected in major depressive disorders[50–52] and that Garner *et al.* found an enlarged pituitary volume prior to the onset of psychotic major depression,[4] further investigation of the disease specificity of pituitary findings is warranted.

Conclusion

Both the ARMS and FESz subjects had significant enlargement of the pituitary gland, presumably reflecting activation of the hormonal stress response during early psychosis. Given that the pituitary gland is a dynamic organ reflecting state-related HPA axis dysregulation, longitudinal study of the pituitary volume and its relation to clinical characteristics, as well as hormone levels, is required to further understand the role of HPA functioning in the emergence of psychosis.

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Brief report

Longitudinal MRI study of the midline brain regions in first-episode schizophrenia

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ABSTRACT

This magnetic resonance imaging (MRI) study investigated the prevalence and size of the adhesio interthalamica (AI) and cavum septi pellucidi (CSP) in 64 first-episode schizophrenia patients and 64 controls, of whom longitudinal data were available for 20 patients and 21 controls. The AI was shorter in the patients and showed longitudinal decline in both groups; there was also a trend for AI atrophy to correlate with negative symptoms. The CSP showed no group difference. These results suggest a role for the AI as a possible neurodevelopmental marker of schizophrenia.

1. Introduction

The adhesio interthalamica (AI), a midline structure connecting the medial surfaces of the thalami, is variable in size among individuals and missing in about 20% of human brains (Carpenter and Sutin, 1983). Previous neuroimaging studies have demonstrated that schizophrenia patients are more likely to have a smaller AI (reviewed by Trzesniak et al., 2011a), possibly reflecting early developmental abnormalities. A large cavum septi pellucidi (CSP) ($\geq$6 mm; Takahashi et al., 2007), which is formed by the incomplete fusion of the septum pellucidi (Rakic and Yakovlev, 1968), may also be related to fetal neurodevelopmental abnormalities in schizophrenia (Trzesniak et al., 2011b). Our previous magnetic resonance imaging (MRI) studies showed smaller AI and a higher rate for it to be absent, but no difference in the size and prevalence of CSP, in a large sample of chronic schizophrenia patients compared with controls (Takahashi et al., 2007, 2008a), but these results may have been partly biased by the effects of medication and illness chronicity. A recent longitudinal MRI study demonstrated the possibility that the size of these midline regions could change during the course of the illness (Trzesniak et al., 2012), whereas Davidson et al. (2012) reported longitudinal stability in the CSP length in first-episode schizophrenia.

This MRI study aimed to replicate our earlier observations described above in a cohort of first-episode schizophrenia and to investigate the changes over time in the size of these midline regions. Given their potential role as neurodevelopmental markers, we posited no diagnosis-by-time interaction in these regions.

2. Methods

2.1. Participants

Sixty-four schizophrenia patients fulfilling the ICD-10 research criteria (World Health Organization, 1993), whose illness duration was 1 year or less (n=48) or under first psychiatric hospitalization (n=16), were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. Sixty-four healthy volunteers were recruited from the community, hospital staff, and university students. The controls were given a questionnaire consisting of 15 items concerning their personal and family histories of illness; none had a personal or family history of psychiatric illness among their first-degree relatives. All subjects were right-handed and physically healthy, and did not have any history of serious head trauma, neurological illness, substance abuse, or serious medical disease. Of the 128 participants, 37 patients and 60 controls were included in our previous cross-sectional studies of the CSP (Takahashi et al., 2007) and AI (Takahashi et al., 2008a). Follow-up MRI data were available for 20 patients and 21 controls; the characteristics of this sub-sample were largely comparable with those of the whole sample of this study (Table 1). The controls were also assessed using the questionnaire at follow-up to ensure that none had any neuropsychiatric disorder during the period between scans.

The patients' clinical symptoms were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative and Positive Symptoms (SANS/SAPS; Andreasen, 1984). The diagnosis of schizophrenia was confirmed in all patients at least 6 months after the illness onset based on

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Table 1
Sample characteristics and brain measurements of the participants.

	Cross-sectional sample			Longitudinal sample		
	Controls	Schizophrenia	Group comparisons	Controls	Schizophrenia	Group comparisons
Male/female	37/27	37/27	Chi-square=0.00, p=1.000	13/8	14/6	Chi-square=0.30, p=0.585
Age (years)	25.1 ± 5.0	24.0 ± 4.7	$F(1, 126)$=1.64, p=0.203	24.5 ± 5.0	23.8 ± 5.0	$F(1, 39)$=0.19, p=0.664
Height (cm)	167.0 ± 7.5	164.9 ± 7.6	$F(1, 126)$=2.60, p=0.109	167.3 ± 7.6	166.2 ± 6.6	$F(1, 39)$=0.27, p=0.606
Education (years)	16.5 ± 2.6	13.5 ± 1.9	$F(1, 126)$=57.55, p<0.001	15.6 ± 2.4	13.0 ± 1.6	$F(1, 39)$=17.24, p<0.001
Parental education (years)[a]	13.2 ± 2.5	13.0 ± 2.0	$F(1, 124)$=0.50, p=0.482	12.8 ± 2.6	12.5 ± 2.1	$F(1, 39)$=0.10, p=0.756
Inter-scan interval (years)	–	–		2.5 ± 0.4	2.7 ± 0.8	$F(1, 39)$=1.30, p=0.261
Onset age (years)	–	23.1 ± 4.7	–	–	22.7 ± 5.1	–
Illness duration at baseline (months)	–	11.2 ± 12.2	–	–	10.2 ± 9.4	–
Medication type (T/AT/mixed)						
At baseline	–	18/43/1[b]	–	–	6/12/2	–
During follow-up	–	–	–	–	3/13/4	–
Medication dose (haloperidol equivalent)						
At baseline (mg/day)	–	10.3 ± 8.8	–	–	14.6 ± 11.7	–
Cumulative dose during follow-up (mg)	–	–	–	–	9852 ± 8727	–
Duration of medication at baseline (months)	–	8.3 ± 12.6	–	–	8.3 ± 10.1	–
SAPS total at baseline	–	27.3 ± 21.9 (N=61)	–	–	33.0 ± 24.0 (N=17)	–
SAPS total at follow-up	–	–	–	–	19.1 ± 17.5 (N=19)	–
SANS total at baseline	–	53.1 ± 25.2 (N=61)	–	–	53.7 ± 27.1 (N=17)	–
SANS total at follow-up	–	–	–	–	38.0 ± 24.0 (N=19)	–
AI absent [N (%)]	7 (10.9)	10 (15.6)	Chi-square=0.61, p=0.435	3 (14.3)	4 (20.0)	p=0.627, Fisher's exact test
AI length at baseline (mm) (median)	8.9 ± 3.5 (10.0)	7.3 ± 3.2 (7.0)	$F(1, 122)$=11.08, p=0.001	8.4 ± 3.5 (8.0)	6.9 ± 3.3 (6.5)	$F(1, 35)$=1.40, p=0.245
AI length at follow-up (mm) (median)	–	–	–	8.1 ± 3.4 (7.0)	6.8 ± 3.1 (6.5)	$F(1, 35)$=1.71, p=0.200
AI change during follow-up (mm)[c]	–	–	–	−0.3 ± 0.6	−0.2 ± 0.7	$F(1, 33)$=1.39, p=0.247
large CSP [N (%)]	8 (12.5)	3 (4.7)	p=0.115, Fisher's exact test	2 (9.5)	1 (5.0)	p=0.578, Fisher's exact test
CSP length at baseline (mm) (median)	4.7 ± 10.1 (2.0)	3.1 ± 6.5 (2.0)	$F(1, 122)$=0.26, p=0.611[d]	4.8 ± 11.4 (2.0)	3.4 ± 5.9 (2.0)	$F(1, 35)$=0.00, p=0.970[d]
CSP length at follow-up (mm) (median)	–	–	–	4.9 ± 11.6 (2.0)	3.2 ± 5.7 (2.0)	$F(1, 35)$=0186, p=0.669[d]
CSP change during follow-up (mm)[c]	–	–	–	+0.1 ± 0.5	−0.2 ± 0.7	$F(1, 33)$=0.10, p=0.753
Intracranial volume (cm^3)	1501.9 ± 150.4	1499.8 ± 147.1	$F(1, 125)$<0.01, p=0.983	1501.1 ± 158.3	1482.2 ± 133.2	$F(1, 38)$=0.08, p=0.774

Values represent means ± S.D.'s unless otherwise stated.
AI, adhesio interthalamica; AT, atypical; CSP, cavum septum pellucidum; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; T, typical.

[a] Data missing for one control and one schizophrenia subjects.

[b] Two patients were medication free at the time of scanning.

[c] Negative value indicates a decrease in length. The statistical analyses reported herein were based on repeated measures ANCOVA with time (baseline, follow-up) as a within-subject variable (see text). The main effect of time was $F(1, 37)$=4.95, p=0.032 for the AI and $F(1, 37)$=0.02, p=0.883 for the CSP.

[d] The CSP measures were log-transformed for statistics because of their skewed distribution (p<0.01, Kolmogorov–Smirnov test). The skewness and kurtosis statistics of baseline CSP length were 4.82 and 24.12 before transformation and 1.00 and 2.49 after transformation, respectively.

information obtained from a detailed chart review. Other clinical information, including cumulative neuroleptic dosage during the study, was also collected in this chart review. Medication and other clinical data are summarized in Table 1.

This study was approved by the Committee on Medical Ethics of Toyama University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

The subjects were scanned on a 1.5-T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160-180 contiguous T1-weighted slices of 1.0-mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time=24 ms; echo time=5 ms; flip angle=40°; field of view=256 mm; and matrix size=256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm^3. The follow-up data were acquired using the same scanner/parameters as described above. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

To assess the AI and CSP, the images were processed using Dr. View software (AJS, Tokyo, Japan) as described elsewhere (Takahashi et al., 2007, 2008a). Briefly, brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure (AC-PC) line. One rater (TT), who was blind to the subjects' identity and time of scan, counted the number of coronal slices where each midline region was clearly seen. The length of the AI and CSP (in mm) was equal to the number of these slices. We considered the AI as present when it could be identified on three or more slices on both coronal and axial views (Takahashi et al., 2008a). A CSP equal to or greater than 6 mm was defined as large on the basis of previous reports (e.g., Nopoulos et al., 1997; Kwon et al., 1998; Kasai et al., 2004). Intra- and inter-rater (TT and KN) intraclass correlation coefficients for the AI and CSP lengths (n=30) in randomly selected brains were over 0.97.

2.3. Statistical analysis

Chi-square tests, or Fisher's exact tests when expected cell sizes were less than five, were used to assess the frequency of the AI and large CSP. The length of each

midline region was analyzed using analysis of covariance (ANCOVA), with intracranial volume (ICV) and age as covariates and with diagnosis and gender as between-subject factors. Gender was used as a between-subject factor on the basis of possible gender effect on the AI size (Allen and Gorski, 1991). The CSP measures were log-transformed because of their skewed distribution (eFig. 1, Table 1). Longitudinal changes were analyzed using repeated measures ANCOVAs with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis and gender as between-subject factors, and time (baseline, follow-up) as a within-subject variable. Post-hoc Scheffé's tests (Scheffé, 1959) were used to follow up these analyses. The relationships between the midline regions (baseline length, absolute length change during scans) and clinical variables were examined by Pearson's partial correlation coefficients controlling for age and ICV. Inter-scan interval and cumulative medication dose were also used as controlling factors for correlational analyses between length change and clinical variables. Statistical analyses reported here were performed using the STATISTICA software package (Statsoft, Tulsa, OK); the statistical modeling was based on its manual (Statsoft, 1994) as in our previous publications (e.g., Takahashi et al., 2009). Statistical significance was defined as $p < 0.05$.

3. Results

There was no group difference in the prevalence of an absent AI (Table 1), but ANCOVA of the baseline AI length revealed significant main effects for diagnosis [$F(1, 122)=11.08$, $p=0.001$] and gender [$F(1, 122)=5.36$, $p=0.022$] but not their interaction. Post hoc analyses showed that the patients had a shorter AI than controls ($p=0.004$) (eFig. 2) and males had a shorter AI than females ($p<0.001$). However, the main effect for diagnosis was not significant when we added medication duration and dose also as covariates [$F(1120)=1.20$, $p=0.276$]. Longitudinal analyses of the AI revealed a significant effect of time [$F(1, 37)=4.95$, $p=0.032$], but no diagnosis-by-time interaction, indicating its atrophy over time in both groups ($p=0.032$). The AI length, but not CSP length, at the baseline was negatively correlated with age for both controls ($r=-0.343$, $p=0.005$) and patients ($r=-0.277$, $p=0.027$). In the patients, the AI length was not correlated with the onset age, illness duration, medication (duration and dose), or total SANS/SAPS scores. The cumulative medication dose did not correlate with the AI change over time. Overall, although not statistically significant [$n=16$, $F(1,15)=2.34$, $p=0.147$], negative symptoms (total SANS score) reduced over time (Table 1), but greater AI atrophy over time was correlated at a trend level with less improvement in negative symptoms ($r=0.619$, $p=0.032$), though this did not survive Bonferroni correction (Dunn, 1961).

For the CSP (length and prevalence), we found no effect of diagnosis, time, or gender (Table 1, eFig. 1). The CSP categories (absent, present, or large) changed during follow-up in one control [from absent to present (1 mm)] and one patient [from present (2 mm) to absent]. The CSP length did not correlate with any clinical variables.

The ANCOVA results of length change over time remained the same for both AI and CSP even when we added baseline medication dose or deleted cumulative medication dose as the covariate.

4. Discussion

Consistent with previous findings in first-episode schizophrenia (Trzesniak et al., 2012) or clinical high-risk subjects (Takahashi et al., 2008b), baseline results in this study demonstrated shorter length of the AI in schizophrenia patients in the early illness stages. A lack of correlation with medication and illness duration, as well as no disease-specific progressive changes, also supports the concept that AI malformation may at least partly represent early neurodevelopmental disturbance in schizophrenia (Weinberger, 1987). On the other hand, we did not identify any differences in the CSP measures between the groups, suggesting that it may not play a major role in the neurobiology of schizophrenia (Takahashi et al., 2007, 2008c).

The present study and a previous (Trzesniak et al., 2012) longitudinal analysis found AI atrophy over time in both schizophrenia and controls, supporting the notion that the AI develops during early gestation, but also undergoes increasing atrophy with age (Rosales et al., 1968; O'Rahilly and Müller, 1990). This study also replicated that men had shorter AI than women (Allen and Gorski, 1991). While the functional significance of the AI, as well as the nature of its atrophy, remains unclear, the midline nuclei of the thalamus including the AI have efferent connections with the amygdaloid nuclei (Graff-Radford, 1997) and are involved in the regulation of the dopamine release of the basal ganglia (Romo et al., 1984). A trend-level correlation between longitudinal AI atrophy and negative symptoms may support a relationship between AI abnormalities and negative symptoms in schizophrenia (Meisenzahl et al., 2000, 2002; Takahashi et al., 2008a), but this effect needs to be replicated. Also, this possible correlation would suggest a role in schizophrenia for accelerated atrophy in AI during adulthood in addition to the hypothesized role as an early neurodevelopmental marker. Although we found no diagnosis-by-time interaction in AI length, it is possible that the reduced AI length apparent at the first episode is due to accelerated AI atrophy at or before illness onset and our sample size or duration is underpowered to examine this effect.

The present study supported the role of the AI as a neurodevelopmental marker of schizophrenia, although possible medication effect on the AI morphology should be further examined. In addition, our longitudinal analyses should be considered preliminary due to the small sample size. For example, in contrast to the negative CSP findings in this study, several previous studies have found CSP abnormalities in schizophrenia (reviewed by Trzesniak et al., 2011b) and Trzesniak et al. (2012) demonstrated significant expansion of the CSP in 52 first-episode patients even during a shorter follow-up period (18 months). As Choi et al. (2008) reported abnormal CSP in subjects at risk for psychosis using the CSP grading system, which integrated CSP length, width, and overall size, the possibility also exists that measuring only the length of the CSP might not be a sensitive enough approach to detect existing changes of the CSP. Another limitation of this study is that neighboring structures are not measured, so it cannot be ruled out that differences in AI are accounted for by differences in thalamic or ventricular volume or orientation. Additional longitudinal studies in a larger cohort in various illness stages (e.g., prodromal and chronic phases) are required to further understand the nature of midline brain abnormalities in the course of schizophrenia.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2012.12.001.

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Letter to the Editor

Altered depth of the olfactory sulcus in subjects at risk of psychosis

Dear Editor,

We read with great interest the letter by Turetsky et al. (2012) concluding that olfactory impairment is a promising biomarker of the psychosis clinical high-risk state. Recent magnetic resonance imaging (MRI) study demonstrated that schizophrenia patients had abnormally shallow olfactory sulci in early illness stages (Takahashi et al., 2013), potentially due to disturbance in olfactory system formation during neurodevelopment. Since it remains unknown whether high-risk subjects exhibit similar changes, we investigated the olfactory sulcus morphology in subjects with at-risk mental state (ARMS).

Twenty-two ARMS subjects diagnosed according to the Comprehensive Assessment of At Risk Mental States (Yung et al., 2005) and 22 controls (Table 1) were recruited as described in detail elsewhere (Nakamura et al., 2013). The ARMS subjects were also assessed using the Beck Depression Inventory (BDI; Beck et al., 1961) and State Trait Anxiety Inventory (STAI; Spielberger et al., 1983) at intake of the Consultation Support Service in Toyama (CAST). Their symptoms were assessed at scanning using the Scale for the Assessment of Negative/Positive Symptoms (SANS/SAPS; Andreasen, 1984). Eighteen ARMS subjects were antipsychotic-naïve, but three were receiving low doses of atypical antipsychotics (risperidone, blonanserin, or aripiprazole) and one was treated with sulpiride at the time of scanning. Five (22.7%) ARMS subjects developed schizophrenia and 17 (77.3%) did not develop psychosis during clinical follow-up (mean follow-up period = 15.6 months, SD = 17.4). All subjects were right-handed and physically healthy at the time of the study, and none had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease. The Committee on Medical Ethics of Toyama University approved this study and written informed consent was obtained for all participants.

Subjects underwent MR imaging at Toyama University Hospital on a 1.5-T Magnetom Vision (Siemens, Erlangen, Germany) with a three-dimensional T1 gradient-echo fast low angle shot protocol (TR = 24 ms; TE = 5 ms; Flip = 40°; FOV = 256 mm; Matrix =256 × 256 pixels; original slice = sagittal; slice thickness =1.0 mm; and voxel size was 1.0 × 1.0 × 1.0 mm). Using the Dr. View software (AJS, Tokyo, Japan), the average depth of the olfactory sulcus (sum of the depth in all slices containing the sulcus/slice number) was measured on reconstructed contiguous coronal images, with a 1.0-mm thickness, perpendicular to the AC–PC line (Takahashi et al., 2013). Its anterior–posterior length (mm) was equal to the number of these coronal slices. High intra- (TT) and inter-rater (TT and YN) intraclass correlation coefficients for the length and depth of the olfactory sulcus in our group (>0.83) have been established previously (Takahashi et al., 2013) using a reliability data set scanned by the same scanner/parameters as in this study.

The olfactory sulcus measures were analyzed using the repeated measures analysis of covariance, with age, intracranial volume (ICV), education, and parental education as covariates, diagnosis and gender as between-subject factors, and hemisphere as a within-subject variable. Post-hoc Scheffé's tests were used. The relationships between the olfactory sulcus measures and clinical variables (BDI, STAI, and SANS/SAPS scores) were examined by Pearson's partial correlation coefficients controlling for age, ICV, education, and parental education. Statistical significance was defined as $p < 0.05$.

The olfactory sulcus depth was significantly shallower in the ARMS subjects bilaterally and deeper in the right hemisphere, whereas its length showed no significant effect involving diagnosis or hemisphere (Table 1). The sulcus depth [F (1,16) = 0.11, p = 0.748] and

Table 1
Demographic and clinical data and brain measures of the at risk mental state (ARMS) individuals and matched controls.

	ARMS (11 M, 11 F)	Controls (11 M, 11 F)	Group comparisons
Age (years)	19.1 ± 4.1	19.4 ± 4.2	F (1, 42) = 0.05, p = 0.830
Height (cm)	162.2 ± 9.5	164.3 ± 8.5	F (1, 42) = 0.62, p = 0.436
Education (years)	11.1 ± 1.6	13.1 ± 2.6	F (1, 42) = 8.99, p = 0.005
Parental education (years)	13.8 ± 1.7	12.4 ± 1.6	F (1, 42) = 7.68, p = 0.008
Medication dose (HPD equiv., mg/day)	2.2 ± 3.1 (n = 4)	–	–
Duration of medication (months)	2.3 ± 4.1 (n = 4)	–	–
Time between intake and scan (days)	50.8 ± 74.4	–	–
Time between scan and onset (months)	8.2 ± 9.9 (n = 5)	–	–
STAI trait at intake[a]	65.3 ± 10.9	–	–
STAI state at intake[a]	58.4 ± 11.3	–	–
BDI at intake[a]	24.1 ± 10.0	–	–
SAPS total at scanning	20.4 ± 10.9	–	–
SANS total at scanning	48.5 ± 19.4	–	–
Intracranial volume (cm^3)	1460 ± 132	1500 ± 146	F (1, 37) = 2.45, p = 0.126
Olfactory sulcus length (mm)			F (1, 36) = 0.71, p = 0.404
Left	43.0 ± 2.7	43.9 ± 2.6	
Right	43.1 ± 3.4	43.9 ± 3.1	
Olfactory sulcus depth (mm)[b]			F (1, 36) = 19.62, p < 0.001
Left	11.6 ± 1.4	13.7 ± 1.0[c]	
Right	12.3 ± 1.0[d]	14.3 ± 1.5[c,d]	

Data are presented as mean ± SD. BDI, Beck Depression Inventory; HPD, haloperidol; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; STAI, State Trait Anxiety Inventory.
[a]Data missing for one participant.
[b]Analysis of covariance showed a significant main effect of hemisphere [F (1,40) = 13.05, p < 0.001].
Post-hoc tests showed: [c]p < 0.001, deeper than in ARMS; [d]p < 0.001, deeper than in left hemisphere.

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