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Letter to the Editor

A two-stage case–control association study between the tryptophan hydroxylase 2 (*TPH2*) gene and schizophrenia in a Japanese population

Dear Editors,

Serotonin has been shown to be involved in neurobiological mechanisms underlying schizophrenia (Abi-Dargham, 2007). The gene encoding tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme in brain serotonin synthesis (Walther et al., 2003), could serve as a candidate gene for schizophrenia. Previous studies have failed to provide evidence for an association between *TPH2* and schizophrenia (De Luca et al., 2005; Higashi et al., 2007; Shiroiwa et al., 2010; Tee et al., 2010; Kim and Yoon, 2011; Serretti et al., 2011; Zhang et al., 2011). However, these studies were performed with relatively small sample sizes and a limited number of markers. A two-stage case–control association study in Japanese individuals was performed to assess whether *TPH2* is implicated in schizophrenia vulnerability.

The present study was approved by the Ethics Committee of each participating institute, and written informed consent was obtained from all participants. The screening population comprised 626 patients with schizophrenia (333 men and 293 women; mean age 39.9 ± 13.9 years) and 620 mentally healthy individuals (317 men and 303 women; mean age 38.2 ± 10.6 years). Controls were identical to our previous association study of *TPH2* with autism spectrum disorders (Egawa et al., 2011). The confirmatory population comprised 2007 patients (1079 men and 928 women; mean age 47.2 ± 14.3 years) and 2195 controls (1165 men and 1030 women; mean age 46.6 ± 13.8 years). Psychiatric assessment was conducted in each participant as previously described (Watanabe et al., 2006).

A total of 17 tagging single nucleotide polymorphisms (SNPs) for *TPH2* (chr12:70617063.70712616) were selected from the HapMap database (http://hapmap.ncbi.nlm.nih.gov/) as previously described (Watanabe et al., 2010a). However, a TaqMan probe for rs1179001 was not designed and, therefore, the SNP was excluded.

The *TPH2* coding regions (RefSeq accession number, NG_008279.1) were resequenced in 101 patients who were included in the screening population using direct sequencing of PCR products (Supplementary Table 1) as previously described (Nunokawa et al., 2010). Of seven sequence variations detected (Supplementary Table 2), a missense variation was rs78162420 (p.S41Y). In addition, we also included rs139896303 (p.R225Q) which was detected in a patient with autistic disorder in our previous study (Egawa et al., 2011).

All SNPs were genotyped using the TaqMan 5′-exonuclease assay (Applied Biosystems, Foster City, CA; Supplementary Table 3) as previously described (Watanabe et al., 2006).

We investigated two common intronic copy number variations (CNVs) of *TPH2*, Variation_113385 and Variation_42978, in the Database of Genetic Variants (http://projects.tcag.ca/variation/). The Variation_113385 was analyzed using the TaqMan real-time PCR assay (Applied Biosystems Assay ID, Hs03806891_cn) as previously described (Watanabe et al., 2010b). The Variation_42978 was genotyped, based on the PCR product size. Forward and reverse primer sequences for amplification were 5′-CTGCATTGCCCACTATGTTC-3′ and 5′-CCCAACCATCTTCTTTCTGC-3′, respectively.

Genotypic associations were tested using the Cochran–Armitage test for trend or the Fisher's exact test. Allelic associations were tested using the χ^2 test or the Fisher's exact test. Power calculation was performed using Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/). Power was estimated using $\alpha = 0.05$, assuming a disease prevalence of 0.01.

We examined 18 SNPs (Table 1) and 2 CNVs (Supplementary Table 4) in the screening population; order and physical locations are shown in Supplementary Fig. 1. We observed potential associations between schizophrenia and three SNPs: rs2129575, rs1487275, and rs17110747 (allelic $p = 0.0117$, 0.0032, and 0.0130, respectively). The rare missense variation rs139896303 (p.R225Q) was detected in two patients as heterozygotes, but not in controls, although the association was not significant. In the confirmatory population, these four SNPs were not significantly associated with schizophrenia (Table 1).

Common *TPH2* SNPs have been tested for associations with schizophrenia (De Luca et al., 2005; Higashi et al., 2007; Shiroiwa et al., 2010; Tee et al., 2010; Kim and Yoon, 2011; Serretti et al., 2011; Zhang et al., 2011). However, previous studies failed to detect significant associations due to the relatively small sample sizes ($n = 70$–720). The present study investigated associations between tagging SNPs and schizophrenia in a Japanese population using two-stage design. In the moderate-scale screening population ($n = 1246$), three common SNPs were demonstrated to be potentially associated with schizophrenia. However, it was not possible to replicate these associations in a large-scale confirmatory population ($n = 4202$). Taken together, these findings suggest that common *TPH2* SNPs do not confer increased susceptibility to schizophrenia.

To the best of our knowledge, no studies have tested rare missense variations of *TPH2* for associations with schizophrenia. The present study resequenced *TPH2* coding regions in 101 patients and detected rs78162420 (p.S41Y). Of note, rs78162420 (p.S41Y) decreases the ability of TPH2 to synthesize serotonin (Lin et al., 2007). This functional variation was not associated with schizophrenia in the screening population.

In addition, rs139896303 (p.R225Q) was examined. In the combined population comprising the screening and confirmatory populations, the Q allele frequencies were 5/5126 in patients and 1/5396 in controls. However, the association was not significant (odds ratio = 5.29, 95% confidence interval = 0.62–45.3). Because the risk allele frequency was extremely low, even a large sample size in the combined population might not provide adequate power to detect an association between rs139896303 (p.R225Q) and schizophrenia. If the genotypic relative risk is set to 5 for heterozygous risk allele carriers under the multiplicative model of inheritance, approximately 6850 patients and 6850 controls are needed to adequately detect the association with a power of 0.80. Further studies should be performed using sufficiently large sample sizes.

Two common intronic CNVs of *TPH2* were not associated with schizophrenia in the screening population. These results did not

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Table 1
Genotype and allele frequencies of SNPs in the screening and confirmatory populations.

Population	Allele [a]	Patients					Controls					p	
dbSNP ID		*n*	1/1 [b]	1/2 [b]	2/2 [b]	MAF	*n*	1/1 [b]	1/2 [b]	2/2 [b]	MAF	Genotype	Allele
Screening													
rs7963717	A/C	625	500	118	7	0.106	618	488	125	5	0.109	0.7683	0.7705
rs11178999	A/G	625	162	297	166	0.503	618	171	298	149	0.482	0.3051	0.2950
rs78162420	C/A	614	566	45	3	0.042	620	566	52	2	0.045	0.6660	0.6579
rs4565946	C/T	626	255	285	86	0.365	619	278	270	71	0.333	0.0948	0.0917
rs2129575	T/G	626	138	309	179	0.533	619	177	287	155	0.482	0.0135	0.0117
rs1386488	A/C	626	516	102	8	0.094	618	518	97	3	0.083	0.3414	0.3386
rs17110489	T/C	626	279	275	72	0.335	619	259	270	90	0.363	0.1384	0.1314
rs139896303	G/A	620	618	2	0	0.002	618	618	0	0	0.000	0.4996 [c]	0.4998 [c]
rs17110566	G/A	626	463	154	9	0.137	618	468	139	11	0.130	0.5990	0.6019
rs11179027	G/C	626	220	293	113	0.415	618	186	313	119	0.446	0.1165	0.1154
rs4760820	C/G	624	488	128	8	0.115	618	475	138	5	0.120	0.7319	0.7361
rs1386498	G/A	473 [d]	187	227	59	0.365	457 [d]	188	201	68	0.369	0.8581	0.8574
rs11179043	G/C	625	475	139	11	0.129	618	462	149	7	0.132	0.8178	0.8198
rs12231356	C/T	625	522	98	5	0.086	617	529	86	2	0.073	0.2131	0.2153
rs1487275	A/C	624	360	231	33	0.238	617	310	256	51	0.290	0.0031	0.0032
rs11179059	C/T	626	234	282	110	0.401	620	189	323	108	0.435	0.0882	0.0879
rs11179064	G/A	623	403	187	33	0.203	617	405	192	20	0.188	0.3518	0.3450
rs17110747	G/A	625	404	187	34	0.204	619	353	228	38	0.246	0.0150	0.0130
Confirmatory													
rs2129575	T/G	1974	561	959	454	0.473	2167	552	1092	523	0.493	0.0645	0.0634
rs139896303	G/A	1942	1939	3	0	0.0008	2080	2079	1	0	0.0002	0.3585 [c]	0.3117 [c]
rs1487275	A/C	1877	1005	745	127	0.266	2040	1075	810	155	0.275	0.4020	0.4034
rs17110747	G/A	1833	1117	638	82	0.218	2066	1241	724	101	0.224	0.4923	0.4947

Abbreviations: MAF, minor allele frequency; SNP, single nucleotide polymorphism.
[a] Major/minor allele.
[b] Genotypes, major and minor alleles are denoted by 1 and 2, respectively.
[c] Calculated using the Fisher's exact test.
[d] Individuals without the deleted allele of Variation_42978.

exclude the possibility that other *TPH2* CNVs – in particular rare, but highly penetrant, CNVs – may play a role in schizophrenia pathogenesis. However, recent genome-wide association studies of CNVs did not detect rare *TPH2* CNVs with large effects on schizophrenia risk (Levinson et al., 2011). These findings suggest that *TPH2* CNVs do not contribute to genetic susceptibility to schizophrenia.

In conclusion, our two-stage case–control study suggests that *TPH2* does not confer an increased susceptibility to schizophrenia in the Japanese population.

Supplementary materials related to this article can be found online at doi:10.1016/j.schres.2012.01.034.

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Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain activity. Previous NIRS studies indicated the oxy-hemoglobin (oxy-Hb) increase during a verbal fluency task (VFT) is attenuated in patients with major depressive disorder (MDD) as compared with healthy controls. However, the possible relationship between depression symptom severity and oxy-Hb change on NIRS has not yet been elucidated. To examine this relationship, we recruited 30 patients with MDD and 30 age-, gender- and intelligence quotient-matched controls. All underwent NIRS during VFT. As expected, the oxy-Hb increase during the task was significantly smaller in patients than in controls. After false discovery rate correction using 31 channels, the mean increase in oxy-Hb during the task showed a significant negative correlation with the total score of the Hamilton Rating Scale for Depression 21-item version (ch25: rho = −.56; FDR-corrected *p*: .001). When each item of the HAM-D21 was examined individually, insomnia early in 9 channels (rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (rho = −.61 to −.57; FDR corrected *p*: .001 to .003) and psychomotor retardation in 12 channels (rho = −.70 to −.44; FDR corrected *p*: .000–.018) showed significant negative correlations with the mean oxy-Hb increase in the right frontal temporal region. Although it is possible that our results were affected by medication, these data suggest reduced right frontal temporal activation on NIRS during VFT is related to the symptom severity of MDD.

1. Introduction

Major depressive disorder (MDD) is a severe and common psychiatric disorder with a lifetime prevalence of 6.7 per 100 (Waraich et al., 2004). Although depressive symptoms per se do not specifically appear in MDD but also in other psychiatric disorders including bipolar disorders, we do not have an objective diagnostic marker to obtain a clear-cut diagnosis for those patients. In Japan, a relatively new neuroimaging method, near-infrared spectroscopy (NIRS) has been approved by the Ministry of Health, Labor and Welfare as a highly advanced medical technology to help distinguish between schizophrenia, depression and bipolar disorders in 2009. Verbal fluency task (VFT) is recommended as an activation task because of a relatively rich store of data. VFT is an easy task to examine the executive function and frequently used in neuroimaging studies (Alvarez and Emory, 2006) and is known to activate prefrontal cortex (PFC) in healthy subjects (Frith et al., 1991; Schlösser et al., 1998). Numerous neuropsychological studies suggest that patients with MDD show executive dysfunction (Gohier et al., 2009; Rose and Ebmeier, 2006; Fossati et al., 2003; Porter et al., 2003; Degl'Innocenti et al., 1998).

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, restraint-free functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain

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function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) changes with a high time resolution (.1 s). The concentrations of oxy-Hb and deoxy-Hb are assumed to reflect the regional cerebral blood volume (rCBV) changes, which was supported by the simultaneous NIRS and PET study (Villringer et al., 1997; Ohmae et al., 2006).

In fact, numerous studies have demonstrated that the oxy-Hb increase in the fronto-temporal regions during a VFT is significantly smaller in patients with MDD than in those with bipolar disorder or healthy controls (Pu et al., 2008; Kameyama et al., 2006; Suto et al., 2004; Matsuo et al., 2002). Moreover, NIRS studies using VFT have also demonstrated frontal lobe dysfunction in schizophrenia (Suto et al., 2004; Takizawa et al., 2008), and panic disorder (Nishimura et al., 2007). However, the relationship between depression symptom severity at the time of examination and oxy-Hb change on NIRS has not yet been clarified.

In neuroimaging studies using other methodologies, focusing on cortex level that NIRS reflects, positron emission tomography (PET) studies found that abnormal reductions of cerebral blood flow (CBF) and metabolism in patients with MDD in PFC (Kimbrell et al., 2002; Bench et al., 1995; Mayberg et al., 1994; Baxter et al., 1989). As for the relationship between executive function and CBF or metabolism, Elliott et al. (1997) showed activation in PFC was significantly attenuated relative to controls during the Tower of London planning task in PET study. In a functional magnetic resonance imaging (fMRI) study, depressed patients showed significant decreased prefrontal activation during VFT (Okada et al., 2003).

As for the relationship between depression symptom severity and frontal lobe function, Brody et al. (1999) found a positive correlation between change in Hamilton Rating Scale for Depression (HAM-D) scores and change in normalized inferior frontal gyrus (IFG) and ventrolateral PFC (VLPFC) metabolism, which indicates that IFG metabolism increased and VLPFC metabolism decreased as depression symptoms became better. Other initial studies also suggest that abnormal functions in dorsolateral PFC (DLPFC) are mood state dependent, attenuated during the depressed mood and reversing during symptom remission (Bench et al., 1995; Mayberg et al., 1994). In contrast, Drevets et al. (2002) showed the persistence of abnormal metabolic deficits using PET measures in the dorsomedial/dorsal anterolateral PFC in MDD during treatment. According to a review by Drevets (2000), a complex relationship exists between depression symptom severity and metabolic activity in the orbital cortex and VLPFC.

Findings obtained by more recent studies investigating cross-sectional relationship between depression symptom severity and brain function assessed by basal regional CBF and metabolism are also inconsistent. For example, Périco et al. (2005) reported that depression symptom severity was negatively correlated with regional CBF (rCBF) in the left amygdala, lentiform nucleus, and parahippocampal gyrus, and positively correlated with rCBF in the right postero-lateral parietal cortex, whereas Milak et al. (2005) showed only positive correlations in bilateral mesiotemporal cortex, parts of the ventral subgenual basal forebrain, and most of the thalamus, hypothalamus, ventral striatum, and midbrain. Accordingly more studies are warranted to clarify the relationship between depression severity and brain activity including frontal lobe function.

In the present study, considering the consistent finding of attenuated oxy-Hb changes during VFT in the fronto-temporal regions in depression, we hypothesized that oxy-Hb changes during VFT in NIRS could be objective indicators of depressive symptom severity. Thus, we used multi-channel NIRS to investigate the relationship between oxy-Hb changes and symptom severity in patients with MDD. Because NIRS can be measured easily and noninvasively in a restraint-free environment over a short amount of time we expect that NIRS can be widely used to assess objectively depressive symptom severity as a clinical examination.

2. Materials and methods

2.1. Subjects

The subjects were 30 patients with MDD, and 30 healthy volunteers matched for age, gender and premorbid intelligence quotient (IQ). Premorbid IQ was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native speakers of Japanese. All MDD subjects were outpatients of the National Center of Neurology and Psychiatry Hospital in Tokyo, Japan. They were diagnosed according to the Structured Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Disorders (SCID-I; First et al., 1995) by experienced psychiatrists. All patients were medicated with antidepressants. Twenty-seven out of 30 patients were prescribed with one or two antidepressants, 16 with SSRIs, 12 with tricyclics, 7 with milnacipran, 5 with tetracyclics, 2 with trazodone and 1 with mirtazapine. In addition, 20 patients were prescribed with anxiolytics, 16 with hypnotics, 7 with mood stabilizers and 9 with antipsychotics (Supplementary Table 1). Daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006) and anxiolytics/hypnotics to that of diazepam (Inagaki and Inada, 2006) for each patient. The controls were healthy volunteers recruited from the same geographical area through advertisements in free local magazines and our website announcement. They were interviewed using the SCID-I for MDD or SCID-NP for healthy volunteers and an unstructured interview for family history, and those individuals who had a current or past history of Axis I psychiatric disorder or a positive family history of Axis I psychiatric disorder within their first degree relatives were excluded. The exclusion criteria for both groups were previous head trauma, neurological illness, a history of electroconvulsive therapy, alcohol/substance abuse or addiction.

After the study procedures had been fully explained, written informed consent was obtained from every participant. This study was approved by the ethics committee of the National Center of Neurology and Psychiatry.

2.2. Clinical assessment

Depressive symptoms and the level of social functioning were evaluated by a single experienced psychiatrist using the GRID Hamilton Rating Scale for Depression 21-item version (GRID HAM-D21; Kalali et al., 2002) and Global Assessment of Functioning scores (GAF; American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data on the same day that the NIRS measurements were conducted. Sleepiness was evaluated as the score on the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).

2.3. Activation task

The activation task was a letter version of VFT similar to that described by Takizawa et al. (2008). During the VFT, changes in oxy-Hb and deoxy-Hb were measured. The VFT consisted of a 30-sec pre-task baseline, a 60-sec VFT, and a 70-sec post-task baseline. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/ and /o/ during the pre-task and post-task baseline periods. For the VFT, the subjects were instructed to generate as many words as possible.

One of the three initial syllables (A; 0–20 s /a/, /to/, or /na/, B; 20–40 s /i/, /ki/, or /se/, C; 40–60 s /o/, /ta/, or /ha/) was randomly

presented on the computer display placed in front of the subjects, every 20 s during the 60-sec task. The number of possible combinations of syllables is 27 (A;3 × B;3 × C;3 = 27). We adopted 15 among the possible combinations. The number of correct words generated during the task was determined as a measure of task performance.

3. NIRS measurements

3.1. NIRS device

We used a 52-channels NIRS (ETG-4000 Optical Topography System; Hitachi Medical Co., Tokyo, Japan) which measures relative changes in oxy-Hb and deoxy-Hb using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). With this system, these Hb values include a differential pathlength factor (DPF). In the NIRS system, "hemoglobin concentration change*DPF" is calculated as a solution to the simultaneous equations based on the Beer–Lambert law, which cannot escape the effect of DPF. Although DPF varies among various brain regions Zhao et al., using a Monte Carlo simulation, reported the estimated DPF variation in the forehead region of adult humans was roughly homogeneous (Zhao et al., 2002).

The distance between a pair of source-detector probes was set at 3.0 cm and each area measured between a pair of source-detector probes was defined as a 'channel'. The NIRS device is considered to measure 'channels' at a 2–3 cm depth from the scalp, that is, at the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003, Toronov et al., 2001).

3.2. Probe positioning and measurement points

The NIRS probes were fixed with 3 × 11 thermoplastic shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The probes can measure Hb values from bilateral prefrontal and temporal surface regions. The measuring points were labeled ch1 to ch52 from right-posterior to left-anterior (Fig. 1). The correspondence between these NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical cranio-cerebral correlations (Okamoto et al., 2004) and presented on the basis of results obtained by the virtual registration method (Tsuzuki et al., 2007).

3.3. Measurement parameters

The rate of data sampling was .1 second (s). The obtained data were analyzed using integral mode; the pre-task baseline was determined as the mean over a 10 s period just prior to the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was then applied to the data between these two baselines. The moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied automatic rejection of data with artifacts separately for each channel (Takizawa et al., 2008).

According to the aforementioned measurement parameters for integral mode, the waveforms of oxy-Hb, deoxy-Hb and total-Hb

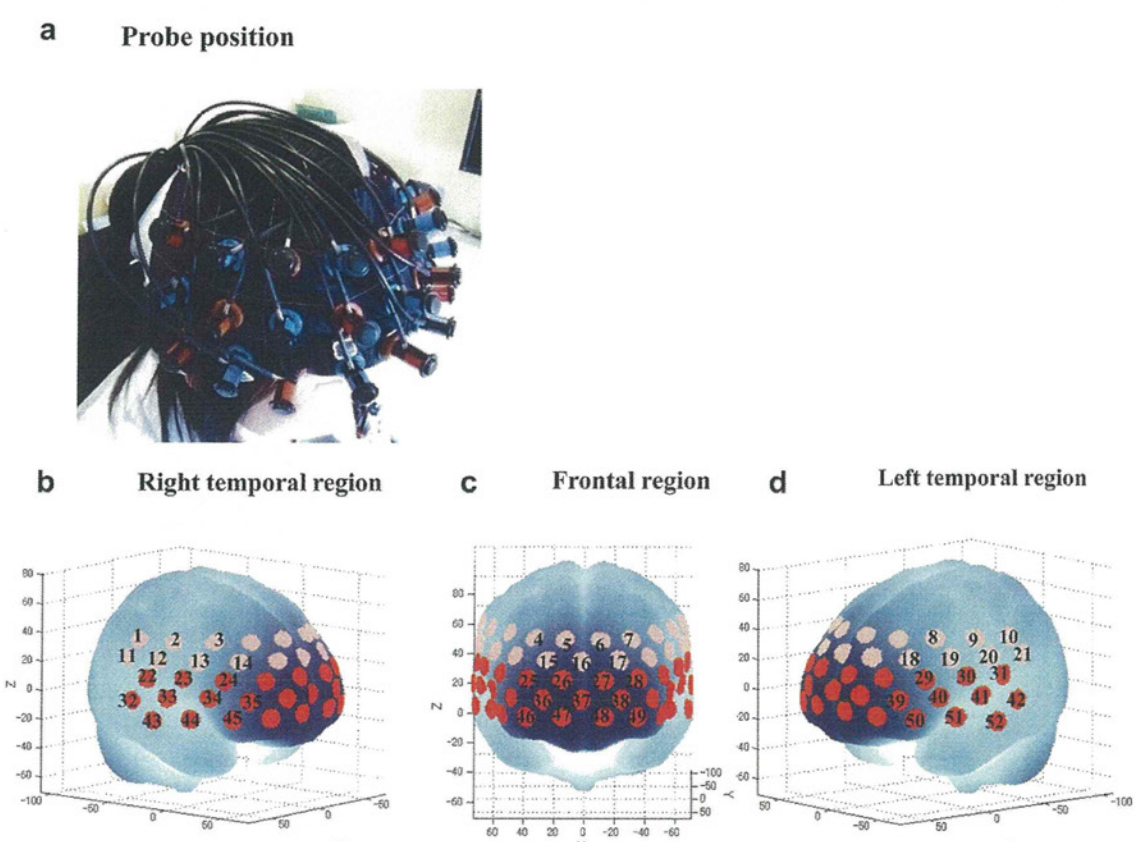

Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS) (a) Probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral frontal regions. (b–d) The 52 measuring positions of the NIRS device are superimposed on the 3D-reconstructed cerebral surface, based on magnetic resonance imaging. The 52 measuring positions are labeled ch1 to ch52, from the right posterior to the left posterior. The dimensional figures b, c and d indicate the right temporal, frontal and left temporal brain regions, respectively. Because acquired NIRS data from the 21 channels in the upper two rows (pink channels) clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ratio seemed to be low, they were excluded from statistical analyses.

changes were acquired from each subject in all 52 channels during VFT.

3.4. Measurement environment

The subjects sat on a comfortable chair in a silent and day-lit room. They were instructed to minimize motions such as head movements, strong biting and blinking during the NIRS measurement, to avoid artifacts.

Data clearly containing motion artifacts, based on both our observations and the NIRS recording, were excluded from further analyses.

4. Statistical analysis

Because acquired NIRS data from the 21 channels in the upper two rows clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ration seemed to be low, they were excluded from statistical analyses.

The χ^2 test or Student's t-test was used to compare proportions and means, respectively, between the MDD and control groups.

As for the analysis of the NIRS data, we focused on oxy-Hb data, since oxy-Hb change (task period − pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean oxy-Hb changes were compared between the two groups (MDD and control) for each channel using Student's t-test. To examine the relationships between oxy-Hb changes and HAM-D21 total scores, HAM-D21 subscale scores, GAF, or other clinical variables, Spearman's rhos were calculated for MDD patients.

All statistical analyses were performed using SPSS for Windows, version 18.0.0 software (SPSS Japan, Tokyo, Japan). A value of $p < .05$ (two-tailed) was considered to be statistically significant. We set the value of q specifying the maximum false discovery rate (FDR) at .05, such that the false positive rate was no more than 5% on average in treating the oxy-Hb data obtained from multiple channels (Singh and Dan, 2006).

5. Results

5.1. Demographic and clinical data of patients and controls

Table 1 summarizes demographic characteristics of the patients and controls. The two groups did not differ significantly in age, gender, handedness, estimated premorbid IQ or SSS.

5.2. Task performance

The number of words generated did not differ significantly among the 15 combinations employed (15 combinations: $F[1, 45] = 1.1$, $p = .39$; three initial syllables: $F[2, 90] = 1.2$, $p = .31$) in either group. The number of generated words during VFT did not differ significantly (patients: 12.3 ± 3.9; controls 13.9 ± 4.3, $t = 1.5$, df = 58, $p = .13$) between the MDD and control groups.

5.3. Group comparison

As shown in Fig. 2, the MDD group had significantly smaller oxy-Hb increases than the control group in 22 channels (ch22–29, ch32–33, ch35–39 and ch44-50; FDR-corrected p: .000–.024) during VFT.

5.4. Relationship with symptom severity at the time of examination

As shown in Fig. 2, there were significant negative correlations between mean oxy-Hb changes during the task and HAM-D21 total scores in one channel (ch25: rho = −.56; FDR-corrected p: .001). Mean oxy-Hb changes during the task period showed significant negative correlations with three individual items of the HAM-D21 subscale scores (Fig. 3); insomnia early in 9 channels (ch23, ch25–27, ch36–37 and ch46–48: rho = −.63 to −.46; FDR corrected p: .000–.014), work and activity in 2 channels (ch44 and ch45: rho = −.61 to −.57; FDR corrected p: .001 to .003), and psychomotor retardation in 12 channels (ch22–24, ch32, ch35–36, ch41, ch43–ch45, ch47 and ch51: rho = −.70 to −.44; FDR corrected p: .000–.018). Mean oxy-Hb changes showed no significant correlations with the remaining HAM-D21 subscale scores (i.e., depressed mood, guilt, insomnia middle, insomnia late, psychomotor agitation, anxiety psychic, anxiety somatic, loss of appetite, somatic symptoms general, sexual interest, hypochondriasis, loss of weight, insight, diurnal variation, and obsessional symptoms;) (Fig. 4).

Furthermore, mean oxy-Hb changes showed no significant correlation with task performance during VFT or other clinical variables, such as age, duration of illness, and sleepiness (data not shown).

5.5. Relationships with medication

There were no significant correlations between the HAM-D21 total score and doses of antidepressants (rho = −.23, $p = .22$) or anxiolytics (rho = .25, $p = .18$). There were significant negative correlations between mean oxy-Hb changes during the task and doses of antidepressants in 6 channels (ch31, ch40–41, ch45, ch50–51: rho = −.57

Table 1
Demographic and clinical data of patients with major depressive disorder and controls.

Demographics	Patients with depression ($n = 30$)	Healthy controls ($n = 30$)	Group difference p-value
Age (years)	36.7 ± 11.6	35.1 ± 9.4	.871
Gender (female/male)	16/14	16/14	1.000
Edinburgh handedness inventory (%)	92.9 ± 9.7	92.0 ± 11.5	.753
Age at onset (years)	30.9 ± 10.8	–	–
Duration of illness (years)	5.8 ± 4.1	–	–
Duration of medication (years)	5.0 ± 3.6	–	–
GRID HAM-D21 total score	16.7 ± 4.8	–	–
Estimated premorbid IQ	105.7 ± 9.5	105.9 ± 8.3	.953
Sleepiness	3.3 ± 1.1	2.9 ± .9	.104
GAF	57.6 ± 9.3		
Medication			
Imipramine equivalent dose (mg/day)	141.9 ± 127.6	–	–
Diazepam equivalent dose (mg/day)	8.5 ± 11.6	–	–

The χ^2 test or t-test was used to compare these variables between patients and controls. GAF, Global Assessment of Functioning; GRID HAM-D21, GRID Hamilton Rating Scale for Depression 21 item; IQ, Intelligence Quotient.

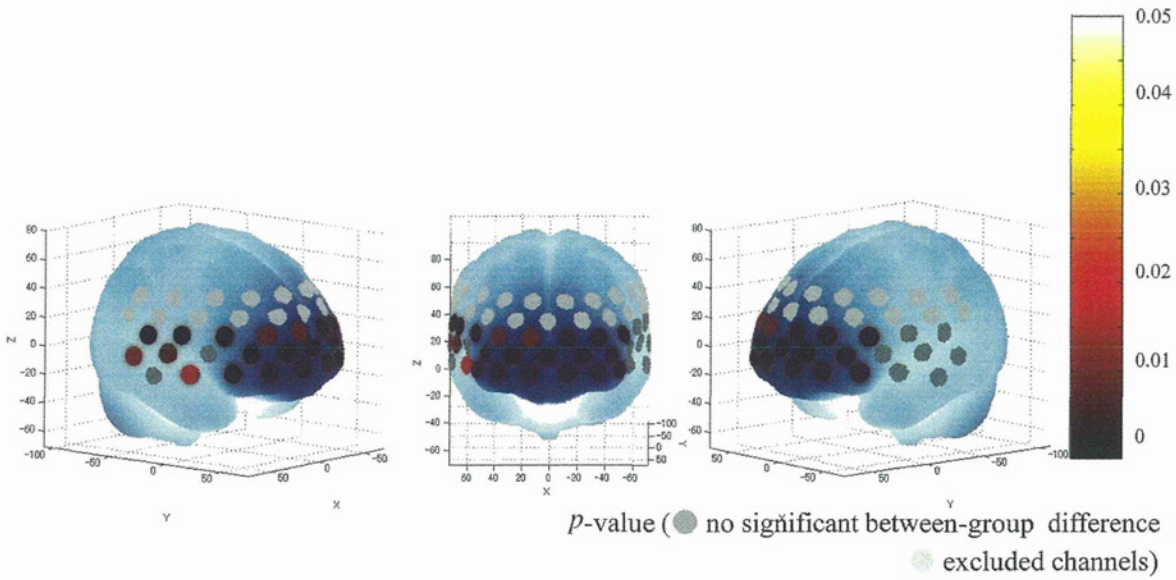

Fig. 2. *p*-value significance map of *t*-tests for oxy-Hb increases in patients with MDD compared with healthy controls during VFT using FDR correction. The warm colored circles represent significantly smaller oxy-Hb increases than in the control group at the channels indicated. There were 22 channels (ch22–29, ch32–33, ch35–39 and ch44–50; FDR-corrected *p*: 000–.024).

to −.48; FDR-corrected *p*: .002 to .007). Mean oxy-Hb changes showed no significant correlations with doses of anxiolytics.

6. Discussion

6.1. Task performance

The number of words generated during the VFT did not differ significantly between patients and controls, which is consistent with the majority of previous studies (Matsuo et al., 2002; Fossati et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Previous studies reported impairment on semantic fluency tasks in depression (Calev et al., 1989; Tarbuck and Paykel, 1995). However, on phonemic fluency task conflicting results patients showing normal or impairment performance in depression (Albus et al., 1996; Degl'Innocenti et al., 1998). Type of psychiatric disorder and task time setting may reflect the discrepancies (Fossati et al., 2003). In the present study, the time setting of VFT was three phonemes within 60 s, that is, 20 s for each phoneme, which differs from the standard VFT usually using 60 s for one phoneme. The time setting condition was designed as it is, so that the subjects were able to keep generating words regularly within the task period to avoid the effect of "not speaking". It is possible that the time setting condition in the present study caused the lack of significant between group-difference in task performance.

6.2. Between-group comparison of oxy-Hb activation

The present study showed oxy-Hb activation during VFT to be significantly smaller in the MDD group than in age-, gender- and IQ-matched healthy controls. This result is essentially consistent with those obtained using NIRS (Matsuo et al., 2002; Herrmann et al., 2004; Suto et al., 2004; Kameyama et al., 2006; Pu et al., 2008), single photon emission computed tomography (SPECT) (Mayberg et al., 1994) or functional magnetic resonance imaging (fMRI) (Okada et al., 2003).

6.3. Relationships with symptom severity at the time of examination

Mean oxy-Hb changes during the task period showed a significantly negative correlation with HAM-D21 total score at ch25. Ch25 is located approximately in the right DLPFC. The finding is in line with some initial studies (Bench et al., 1995; Mayberg et al., 1994) which suggest that abnormal functions in DLPFC are mood dependent. However, other more recent studies investigating cross-sectional relationship between depression psychopathology and brain function do not coincide with our result (Périco et al., 2005; Milak et al., 2005). One of the reasons for the discrepancy may arise from the different methodologies; in the present study we adopted VFT for activation whereas the previous studies observed the basal activity with no activation task. Although speculative as it is, the activation of PFC by VFT may have led to the significant relationship between oxy-Hb changes and depression symptom severity in the right DLPFC.

More interestingly, mean oxy-Hb changes during the task period showed significant negative correlations with three individual HAM-D21 items in a wider area than they showed with HAM-D21 total scores; insomnia early in nine, work and activity in two and psychomotor retardation in twelve channels. The nine channels correlating with "insomnia early" were located approximately in the right pre-motor area, DLPFC and frontopolar and orbitofrontal areas. The two channels correlating with "work and activity" were located approximately in the right DLPFC and temporopolar area. The twelve channels correlating with "psychomotor retardation" were located broadly in the fronto-temporal areas with right hemispheric dominance. Although these findings should be treated with care given the exploratory nature of multiple analyses, it is noteworthy that at least some subscale scores of HAM-D21 appeared to show stronger relationship with oxy-Hb changes than HAM-D21 total scores. It has been pointed out that HAM-D17 and/or HAM-D21 are not necessarily unidimensional, and thus not adequate to assess depression severity (Bagby et al., 2004). Licht et al. (2005) showed that a set of the HAM-D containing six subscales constitute a unidimensional scale measuring severity of

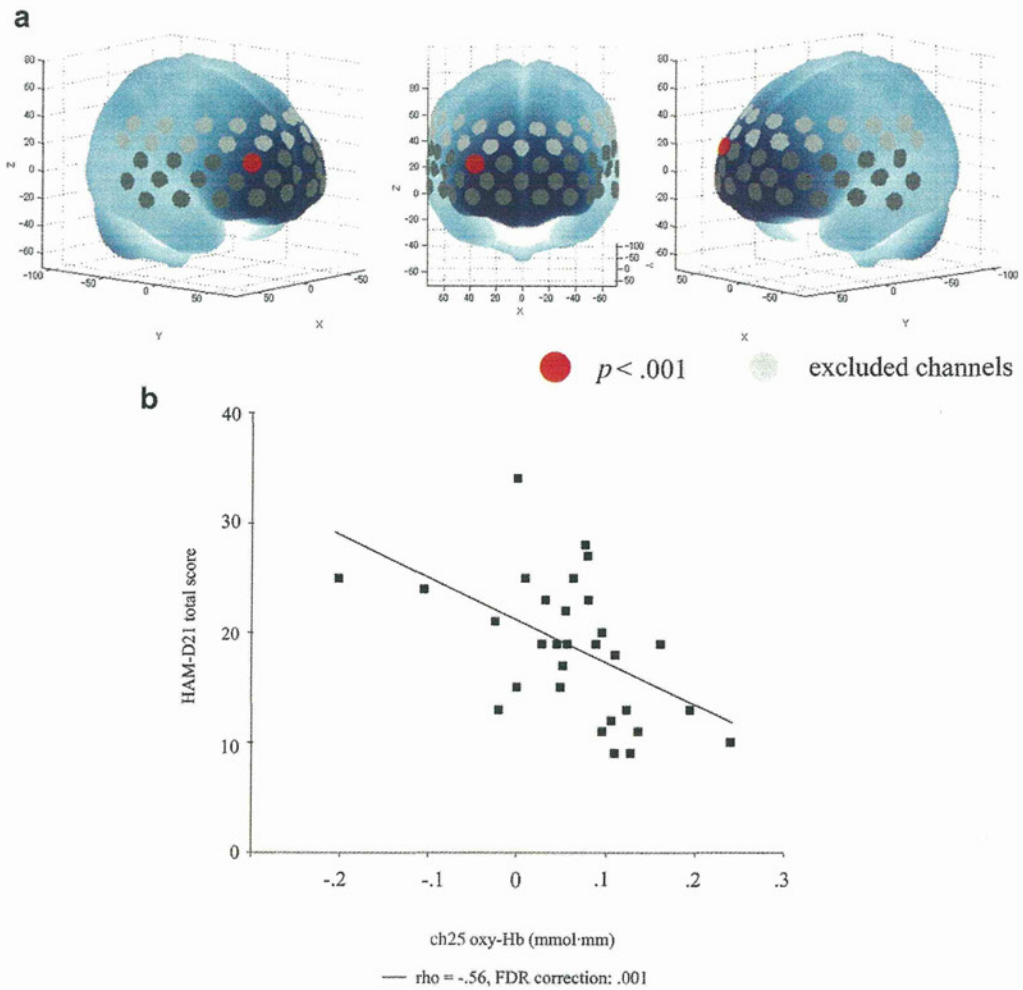

Fig. 3. (a) The channels with a significant correlation between oxy-Hb changes and HAM-D21 total score after FDR correction. (b) Scatter graph showing the relationship between HAM-D21 total scores and oxy-Hb activation in ch25.

depression, whereas the remaining items covering neurovegetative symptoms showed a problematic response somewhat insensitive to depression severity. In fact, the multidimensionality was highlighted in the unstable factor structure, which was demonstrated by a failure to replicate a single unifying structure across studies (Bagby et al., 2004). The relatively strong relationship indicated between HAM-D21 subscale scores and oxy-Hb changes in divergent areas, compared to HAM-D21 total scores may be due to the multidimensional properties of HAM-D21. Graff-Guerrero et al. (2004) also demonstrated that each HAM-D subscale score showed a significant correlation with the basal CBF in variant areas, in some cases showing positive correlation and others negative.

6.4. Relationships with medications

As all patients were taking antidepressants at the time of evaluation, the medication effect could not be ignored. Yet, there was no significant relationship between daily dose levels of antidepressants and the HAM-D21 total score. Although daily dose levels of antidepressants showed significant negative correlations with oxy-Hb changes in six channels, ch25, where a significant correlation between oxy-Hb changes and HAM-D21 total scores was observed, was not included in the six channels. Therefore, we suspect that the effect was small, if at all.

PET has been used to demonstrate that antidepressant medication normalizes both over-activity and under-activity in the frontal cortex (Kennedy et al., 2001, 2007; Mayberg et al., 2000; Goldapple et al., 2004). Unfortunately, our results could not clarify the relationship between medication and brain activation because our analysis was based on cross-sectional data. Although our data may reflect the more restraint-free, natural setting than those using fMRI or PET, further studies in drug-naïve patients are required to draw any conclusions as to the possible effects of medication on brain activation as measured by NIRS. Longitudinal studies investigating the relationship between the change in oxy-Hb data and symptom severity scores with a larger sample size are warranted to reach a conclusion on this matter.

The results of this study must be interpreted with caution due to certain limitations. First, because the analysis was based on cross-sectional data, causality cannot be determined. Longitudinal studies are needed to assess cause-and-effect relationships. Second, our sample size was not large, and is thus subject to type II error. Further studies with larger numbers of MDD patients are required. Finally, owing to the multidimensional properties of HAM-D21, assessment of depression symptom severity using HAM-D21 total scores may not be adequate, and thus, other scales such as Montgomery Asberg Depression Rating Scale (MADRS) or Beck Depression Inventory (BDI) should be tested in the future study.

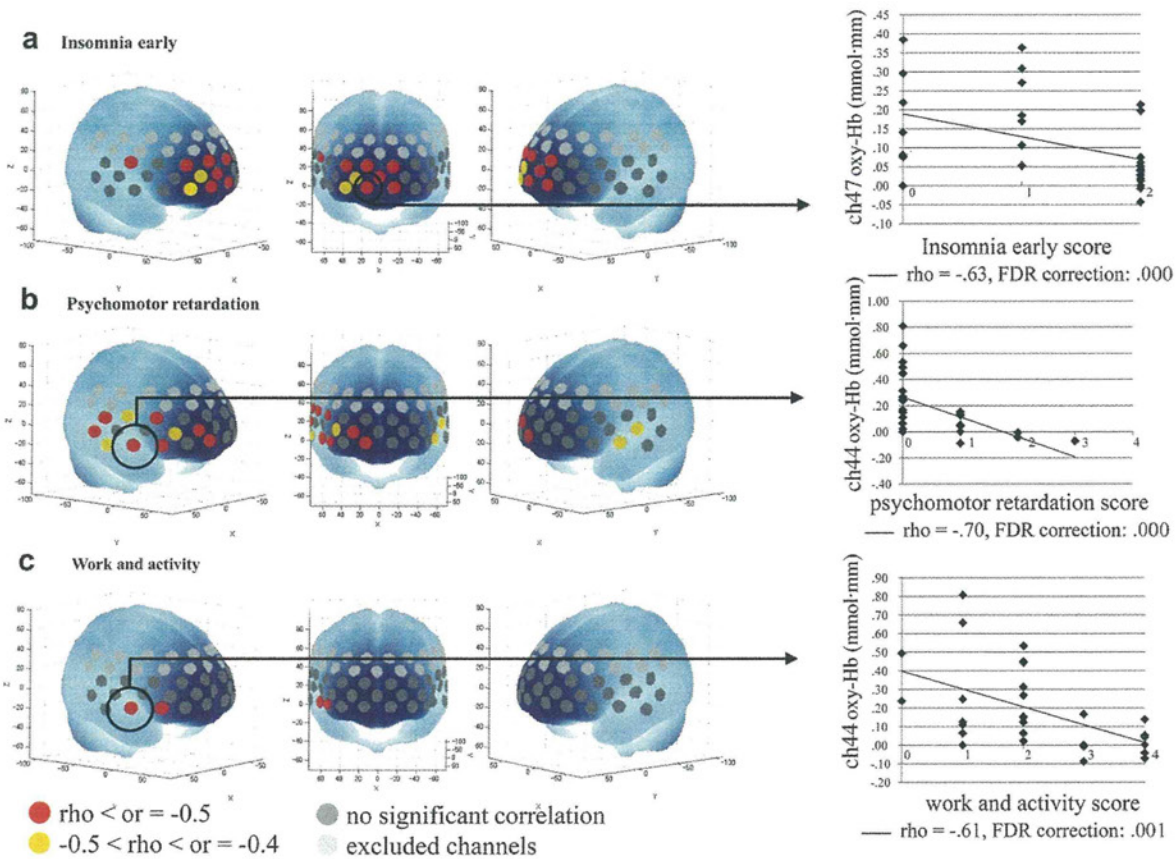

Fig. 4. rho-value map for the correlation between oxy-Hb activation in MDD patients and three individual HAM-D21 subscale scores after FDR correction. (a) insomnia early, (b) psychomotor retardation, and (c) work and activity.

7. Conclusion

In this study, we confirmed that the increase in oxy-Hb during a VFT task is significantly smaller in MDD than in age- and gender-matched healthy subjects. This difference could not be explained by a difference in task performance or premorbid IQ. The blunted increase in right DLPFC was associated with the symptom severity of MDD and therefore oxy-Hb changes during VFT in this region may be a state-dependent marker of depression.

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Contributors

T. Noda designed the study, wrote the protocol, assessment of depression severity, literature searches, statistically analyzed the data, and wrote the first draft of the manuscript. T. Matsuda was involved in patient recruitment and assessment of depression severity. H. Kunugi and S. Yoshida wrote the final version of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2012.04.001.

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Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia

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ABSTRACT

Background: Accumulating evidence indicates that oxytocin plays an important role in social interactions. Previous studies also suggest altered oxytocin function in patients with schizophrenia and depression. However, few studies have examined the central oxytocin levels in these disorders.
Methods: Cerebrospinal fluid (CSF) oxytocin levels were measured by ELISA in male participants consisting of 27 patients with schizophrenia, 17 with major depressive disorder (MDD), and 21 healthy controls.
Results: CSF oxytocin levels of patients with schizophrenia or MDD did not differ significantly with healthy controls. The antidepressant dose or the Hamilton depression rating scale score did not significantly correlate with the oxytocin levels in MDD patients. CSF oxytocin levels in schizophrenic patients significantly negatively correlated with second generation antipsychotic dose ($r=-0.49$, $P=0.010$) but not with first generation antipsychotic dose ($r=-0.13$, $P=0.50$). A significant correlation was observed between oxytocin levels and negative subscale of PANSS ($r=-0.38$, $P=0.050$). This correlation remained significant even after controlling for second generation antipsychotic dose ($r=-0.47$, $P=0.016$).
Conclusions: We obtained no evidence of altered CSF oxytocin levels in patients with schizophrenia or those with MDD. However, lower oxytocin levels may be related to higher second generation antipsychotic dose and more severe negative symptoms in schizophrenia.

1. Introduction

Oxytocin is produced in the supraoptic and paraventricular nuclei of hypothalamus and is secreted into the blood stream from the posterior pituitary. Its release is induced by a variety of stressful stimuli, including noxious stimuli, conditioned fear, and exposure to novel environments (Onaka, 2004). Accumulating evidence indicates that oxytocin plays an important role in social interactions (Lim and Young, 2006; Bartz et al., 2010). Deficits in social functioning observed in psychiatric disorders including schizophrenia (Couture et al., 2006; Sparks et al., 2010) and mood disorders (Inoue et al., 2004; Montag et al., 2010; Wolkenstein et al., 2011) imply the possible involvement of oxytocin in the pathophysiology of these disorders.

Many studies have investigated the possible link between oxytocin and psychiatric disorders. Some previous studies reported altered oxytocin function in patients with schizophrenia (Linkowski et al., 1984; Beckmann et al., 1985; Mai et al., 1993). Higher plasma oxytocin levels in schizophrenic patients were associated with lower symptom severity (Rubin et al., 2010). A clinical study showed that administration of this hormone ameliorated symptoms of schizophrenia (Feifel et al., 2010). In a preclinical study, systemically administered oxytocin reversed prepulse inhibition deficits induced by amphetamine and the phencyclidine analog in rats (Feifel and Reza, 1999). Oxytocin dysfunction has been implicated in the pathophysiology of depression as well. Two studies have shown that peripheral oxytocin levels and depressive symptoms were significantly correlated in patients with major depressive disorder (MDD) (Scantamburlo et al., 2007; Cyranowski et al., 2008). Moreover, oxytocin knock-out mice have shown dysregulated stress responses to psychological stimuli (Mantella et al., 2005) and enhanced anxiety behaviors (Mantella et al., 2003).

Oxytocin secreted from the pituitary gland generally does not re-enter the brain through the blood-brain barrier (Ermisch et al., 1985). Therefore, the behavioral effects of oxytocin are likely to be due to the release from centrally projecting oxytocin neurons. Since

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oxytocin in the nervous system can be transported to blood (Durham et al., 1991), peripheral oxytocin levels may reflect brain levels to some extent. However, central and peripheral oxytocin is regulated independently, and the half-life of oxytocin is less than 5 minutes in the blood (Ryden and Sjoholm, 1969) while that in the brain is 19.1 - minutes (Durham et al., 1991). Therefore, measurement in the CSF is necessary for the direct assessment of central oxytocin levels.

To our knowledge, two studies have previously examined the cerebrospinal fluid (CSF) levels of oxytocin in patients with schizophrenia. One reported elevated oxytocin levels in schizophrenia compared with controls (Beckmann et al., 1985), while the other did not obtain such a finding (Glovinsky et al., 1994). Only one study has examined the CSF levels of oxytocin in patients with depression, in which no difference was found compared with controls (Pitts et al., 1995). No study to date has examined the association of CSF oxytocin levels with symptom severity of these disorders. Since symptom severity forms a continuous spectrum ranging from mild to severe state, an association with the severity of the disease would suggest that oxytocin levels reflect the state of the disease.

In the present study, the oxytocin levels in the CSF of patients with schizophrenia and those with depression were measured and compared to that of healthy controls. Furthermore, we investigated the correlation between CSF oxytocin levels and symptom severity of these disorders. From the findings of previous studies examining peripheral oxytocin levels (Scantamburlo et al., 2007; Rubin et al., 2010), we hypothesized that CSF oxytocin levels would be lower in patient groups compared to healthy controls and that symptom severity would be negatively correlated with the oxytocin levels.

2. Materials and methods

2.1. Subjects

Participants were 27 patients with schizophrenia (mean age (standard deviation): 42.6 (8.5) years), 17 patients with major depressive disorder (MDD) (age: 39.5 (8.0) years), and 21 healthy controls (age: 38.3 (15.3) years). Demographic and clinical characteristics of the subjects are summarized in Table 1. All subjects were males to avoid gender effects and were biologically unrelated Japanese recruited from the outpatient clinic of the National Center of Neurology and Psychiatry Hospital, Tokyo, Japan or through advertisements in free local information magazines and by our website announcement. None of the healthy controls were on psychotropic medication, while 70.6% of the patients with MDD were treated with antidepressant medication at the time of the study. Most of the schizophrenic patients were prescribed antipsychotic medication, and all of those prescribed antipsychotics were on the medication for more than 3 years. Consensus diagnosis by at least 2 psychiatrists was made for each patient according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria (American Psychiatric Association, 1994), on the basis of unstructured interviews and information from medical records. The controls were healthy volunteers with no current or past history of psychiatric treatment and were screened using the Japanese version of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998; Otsubo et al., 2005) by a research psychiatrist to eliminate the possibility of any axis I psychiatric disorders. Participants were excluded if they had prior medical histories of central nervous system diseases or severe head injury or if they met the criteria for substance abuse or dependence or mental retardation. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After describing the study, written informed consent was obtained from every subject.

2.2. Clinical measures

Schizophrenic symptoms and depressive symptoms were assessed immediately after the lumbar puncture by an experienced research psychiatrist using the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Yamada et al., 1991) and the Japanese version of the GRID Hamilton Depression Rating Scale, 17-item version (HAMD-17) (Hamilton, 1967), which have both been demonstrated to show good inter-rater reliability (Igarashi et al., 1998; Tabuse et al., 2007). Medication status at the time of lumbar puncture was recorded. Daily doses of antipsychotics in patients with schizophrenia and antidepressants in patients with MDD were

Table 1
Demographic and clinical characteristics.

	Controls ($N=21$)	Schizophrenia ($N=27$)	Depression ($N=17$)	Analysis
Age (years)	38.3 (15.3)	42.6 (8.5)	39.5 (8.0)	ANOVA: $F=0.97$, n.s.
BMI	23.9 (4.1)	26.0 (6.2)	23.9 (4.5)	ANOVA: $F=1.06$, n.s.
Duration of illness (years)		16.3 (9.8)	7.7 (7.3)	t-test: $t=2.8$, $P<0.01$
Treatment duration (years)		15.5 (9.1)	5.8 (6.9)	t-test: $t=3.4$, $P<0.01$
Medication status				
on antipsychotic medication				
first generation (%)	0	59.3	11.8	
second generation (%)	0	66.7	23.5	
first and/or second generation (%)	0	96.3	35.3	
on antidepressant medication (%)	0	25.9	70.6	
on benzodiazepine medication (%)	0	81.5	76.5	
on mood stabilizer medication (%)	0	14.8	5.9	
CP equivalent dose				
first generation (mg/day)		361.8 (445.0)		
second generation (mg/day)		402.4 (498.3)		
total (mg/day)		764.2 (591.6)		
IMI equivalent dose (mg/day)			167.2 (141.5)	
PANSS				
Positive symptoms score		12.5 (3.8)		
Negative symptom score		16.0 (5.8)		
General symptom score		6.8 (1.3)		
Total score		55.6 (12.6)		
HAMD-17 score			13.4 (9.6)	

Values are shown as mean (standard deviation).
BMI: body mass index; CP: chlorpromazine; IMI: imipramine.
PANSS: Positive and Negative Syndrome Scale; HAMD-17: 17 item Hamilton Rating Scale for Depression.
ANOVA: analysis of variance; n.s.: not significant.

converted to chlorpromazine and imipramine equivalent doses, respectively, using published guidelines (Inagaki et al., 1999).

2.3. Lumbar puncture and oxytocin assay

Lumbar puncture was performed with the subject in the left decubitus position. CSF was withdrawn from the L3–L4 or L4–L5 interspace. After the removal of 2 ml of CSF, a further 6 ml of CSF was collected and immediately transferred on ice to be centrifuged at 4 °C and aliquoted for storage at −80 °C until assay. CSF oxytocin levels were analyzed using a commercial ELISA kit (Enzo Life Sciences, INC., NY). Using the results from two separate runs of standard concentrations, the inter-assay coefficient of variation (CV) was less than 10%.

2.4. Statistical analysis

Statistical differences between groups were calculated using Student's *t*-test, Welch's *t*-test, or one-way analysis of variance (ANOVA). Correlations were assessed using Pearson's correlation coefficient. Since the CSF oxytocin levels were not normally distributed, log transformation was applied prior to statistical analyses to achieve normal distribution. Because previous studies suggest that some antipsychotic and antidepressant medications increase oxytocin secretion (Uvnas-Moberg et al., 1992, 1999), chlorpromazine and imipramine equivalent doses were examined as possible confounders. Statistical analyses were performed using the Statistical Package for the Social Sciences version 11.0 (SPSS Japan, Tokyo, Japan). All statistical tests were two-tailed, and $P<0.05$ indicated statistical significance.

3. Results

Fig. 1 shows the CSF oxytocin levels in each diagnostic group. A one-way ANOVA using the transformed oxytocin levels as the dependent variable indicated no significant difference between diagnostic groups ($F=1.08$, $P=0.35$). The transformed oxytocin levels showed no significant correlation with age or body weight. Figs. 2 and 3 show the relation of CSF oxytocin levels with symptom severity and psychotropic dose, respectively. The antidepressant dose or the HAMD-17 score did not significantly correlate with the transformed oxytocin levels in patients with MDD (antidepressant dose: $r=-0.15$, $P=0.57$; HAMD-17: $r=-0.19$, $P=0.46$). The transformed oxytocin levels were significantly negatively correlated with negative subscale of PANSS ($r=-0.38$, $P=0.050$). Correlations between transformed oxytocin levels and other subscales of PANSS were not statistically significant. The transformed oxytocin levels in schizophrenic patients were significantly negatively correlated with chlorpromazine equivalents of total antipsychotic dose ($r=-0.51$, $P=0.0064$) and second generation antipsychotic (SGA) dose ($r=-0.49$, $P=0.010$) but not with chlorpromazine equivalents of first generation antipsychotic (FGA) dose ($r=-0.13$, $P=0.50$). Those prescribed SGA had significantly lower CSF oxytocin levels compared to those not prescribed SGA (Welch's *t* test: $t=2.6$, $df=10.4$, $P=0.024$). Comparison between patients prescribed and not prescribed FGA did not yield significant difference (Student's t test: $t=1.1$, $df=25$, $P=0.27$). Although none of the subscales of PANSS were correlated with FGA, SGA, or total chlorpromazine equivalent dose in the present study (all $P>0.1$), a previous study (Sim et al., 2009) reported an association between antipsychotic dose and the severity of positive as well as negative symptoms of schizophrenia. Therefore, we considered antipsychotic dose as a confounding factor for the association between oxytocin levels and symptom severity. Thus, we also examined the correlation between the oxytocin levels and PANSS scores controlling for prescribed antipsychotic dose. Partial correlation between transformed oxytocin levels and negative subscale of PANSS, removing the linear effects of total antipsychotic dose, was statistically significant ($r=-0.39$, $P=0.047$). Removing the linear effects of SGA dose instead of total antipsychotic dose also resulted in significant correlation of transformed CSF oxytocin levels with negative subscale ($r=-0.47$, $P=0.016$) as well as with total PANSS score ($r=-0.47$, $P=0.016$). SGA dose-controlled partial correlations between transformed oxytocin levels and other subscales of PANSS were not statistically significant (positive subscale: $r=-0.24$, $P=0.23$; general subscale: $r=-0.33$, $P=0.099$).

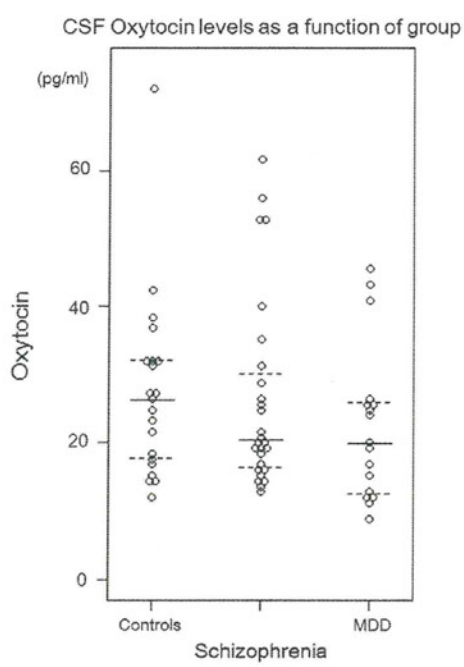

Fig. 1. Cerebrospinal fluid oxytocin levels as a function of group. The cerebrospinal fluid oxytocin levels in healthy controls and patients with schizophrenia and major depressive disorder are shown. Solid bars indicate median values and the dotted lines indicate interquartile range. No significant difference was observed between the diagnostic groups.

4. Discussion

Consistent with some previous studies (Glovinsky et al., 1994; Pitts et al., 1995), CSF oxytocin levels did not significantly differ between healthy controls and patients with schizophrenia and MDD. However, the present results showed that higher levels of CSF oxytocin may be associated with less severe symptoms of schizophrenia.

The observed negative correlation between antipsychotic dose and CSF oxytocin levels points to the possibility that antipsychotic medication lowers oxytocin levels. A recent study suggests that an inhibitory feedback loop may exist between prolactin-secreting lactrophs and oxytocinergic paraventricular neurons (Sirzen-Zelenskaya et al., 2011). Therefore, the disinhibition of prolactin secretion due to the D_2 receptor blockade by antipsychotics may have resulted in the suppression of oxytocin secretion. This, however, does not explain the stronger correlation of SGA dose compared to FGA dose. Kiss et al (2010) showed that SGAs have a more potent influence than haloperidol on the activity of oxytocin magnocellular neurons. This also seems contradictory to the present finding that SGA is negatively correlated with oxytocin levels. An alternative explanation for this negative correlation is that patients with low oxytocin levels may respond poorly to antipsychotic medication, and thus, higher dose was prescribed to such patients. Nevertheless, despite the relatively strong correlation with the antipsychotic dose, the cross-sectional design of the present study hinders any causal inferences. One previous study (Glovinsky et al., 1994) demonstrated that CSF oxytocin levels were unchanged by antipsychotic medication. Thus, further investigation is necessary to elucidate the effects of antipsychotic medication on oxytocin levels.

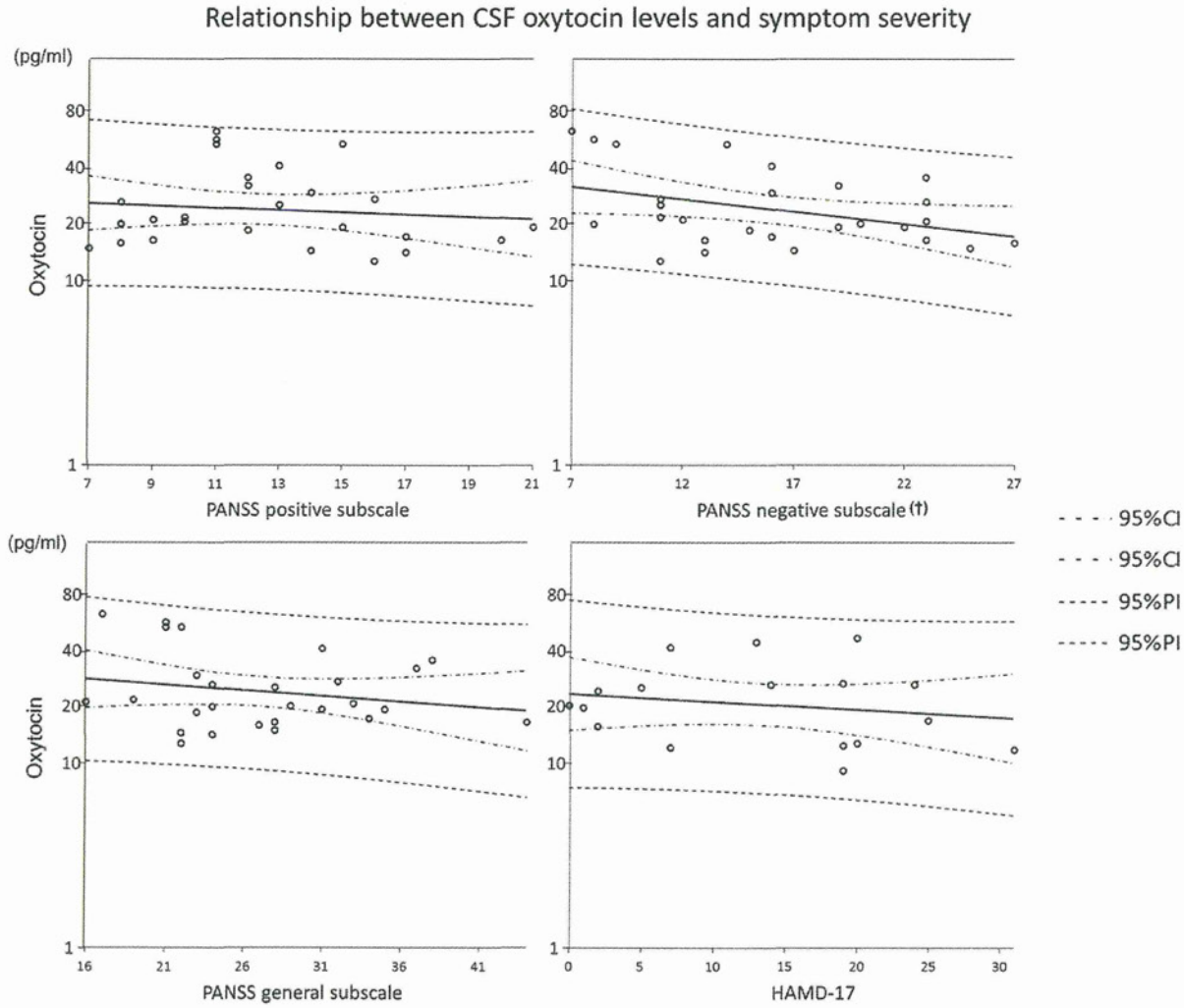

Fig. 2. Relationship between cerebrospinal fluid oxytocin levels and symptom severity. The association between cerebrospinal oxytocin levels and symptom severity is shown. Oxytocin levels are shown in logarithmic scale. Solid lines indicate fitted regression lines, unevenly dashed lines indicate 95% confidence intervals, and evenly dashed lines indicate 95% prediction intervals. (†): Correlation at significance level of $P<0.05$. PANSS: Positive and Negative Syndrome Scale, HAMD-17: Hamilton Depression Rating Scale, 17-item version, 95%CI: 95% confidence interval, 95%PI: 95% prediction interval.

The present results showed that the negative symptoms of schizophrenia were negatively correlated with CSF oxytocin levels. The correlation coefficient between CSF oxytocin levels and total PANSS score was also significant, controlling for SGA dose. Rubin et al. (2010) reported that higher peripheral oxytocin levels were associated with more prosocial behaviors in female patients with schizophrenia. Furthermore, previous studies have demonstrated improvement of social behaviors with administration of intranasal oxytocin (Macdonald and Macdonald, 2010; Pedersen et al., 2011). Since strong relationships between negative symptoms and social difficulties have been demonstrated in schizophrenia (Weinberg et al., 2009), the present finding associating higher CSF oxytocin levels with lower negative subscale is in accord with what has previously been described for peripheral oxytocin. Whether the peripheral oxytocin levels reflect the CSF oxytocin levels, or whether a different mechanisms of action in the brain and the peripheral result in a similar effect, remains to be explored.

Previous studies examining CSF oxytocin levels in patients with schizophrenia (Beckmann et al., 1985; Glovinsky et al., 1994) and depression (Pitts et al., 1995) showed mean oxytocin levels of less than 10 pg/ml, which is lower than that in the present study (>20 pg/ml). Such outcome may have resulted from some of the methodological differences between previous studies and the present one. Previous three studies measured oxytocin levels using radioimmunoassay (RIA), while the present study used a commercially available ELISA kit. A recent study that used the same ELISA kit to measure CSF oxytocin levels (Heim et al., 2009) also demonstrated higher levels of oxytocin (mean oxytocin levels of 17 pg/ml in women without a history of emotional abuse) compared to the previous studies using RIA. Thus, the different measurement techniques may have influenced the values.

A number of other methodological differences exist between the present study and previous ones examining CSF oxytocin levels (Beckmann et al., 1985; Glovinsky et al., 1994; Pitts et al., 1995). One of the major differences was that the present study did not require fasting prior to lumbar puncture, while Beckmann et al (Beckmann et al., 1985) collected CSF in patients with schizophrenia after 12 hours fasting. Although a previous study (Challinor et al., 1994) reported that peripheral oxytocin levels were not affected by 20 hours of fasting, the influence of fasting on CSF levels is unknown. Furthermore, Beckmann et al used Research Diagnostic Criteria to select a patient group consisting entirely of paranoid schizophrenia. Such difference in composition of participants may have affected the outcome of the study by Beckmann et al (1985), which showed significantly higher CSF oxytocin levels in schizophrenic patients compared to healthy controls. The findings by Glovinsky et al (1994) and Pitts et al (1995) were consistent with the present study in that no significant difference in CSF oxytocin levels was found between patients and controls. However,

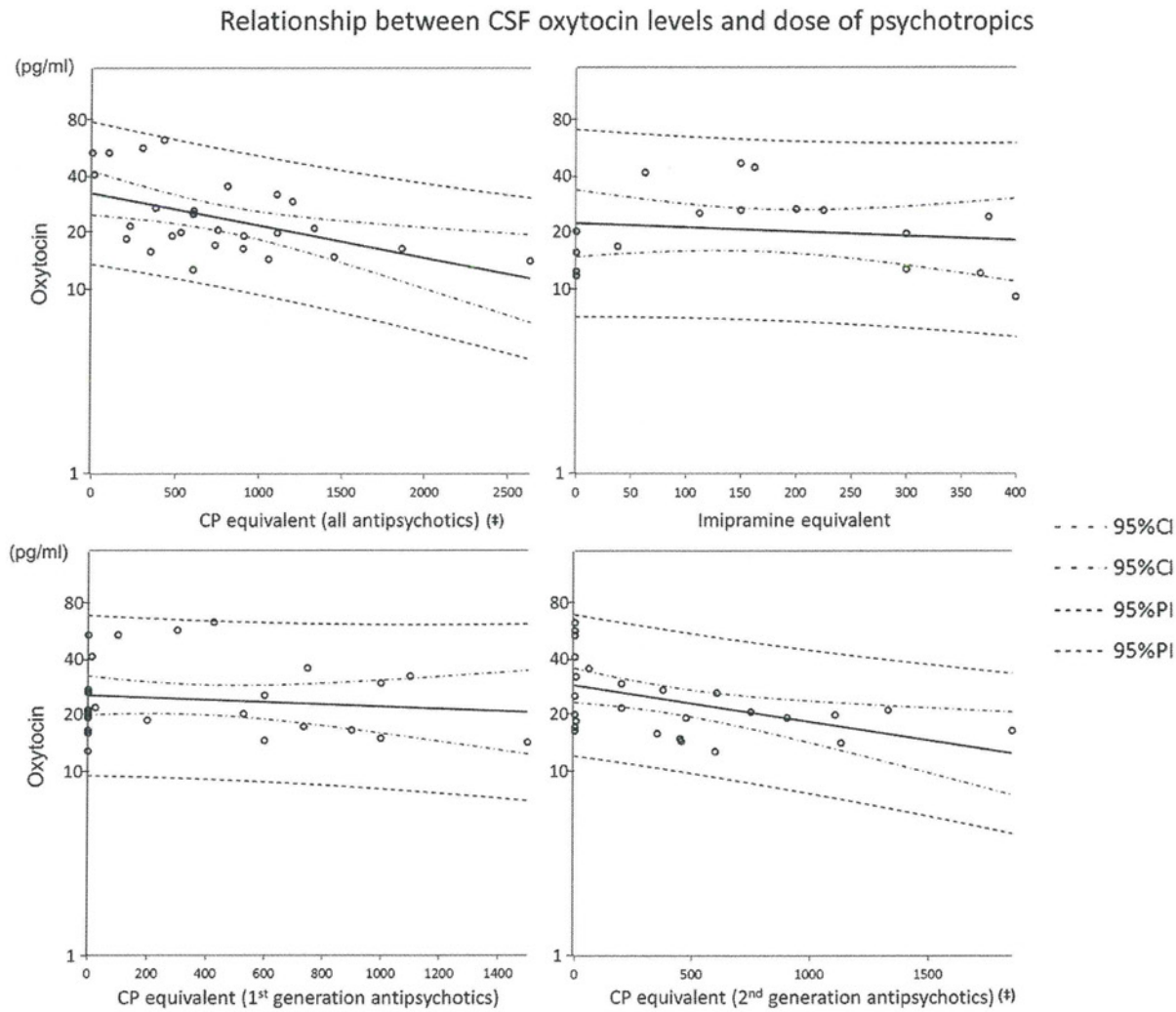

Fig. 3. Relationship between cerebrospinal fluid oxytocin levels and dose of psychotropics. The association between cerebrospinal oxytocin levels and dose of psychotropics is shown. Oxytocin levels are shown in logarithmic scale. Solid lines indicate fitted regression lines, unevenly dashed lines indicate 95% confidence intervals, and evenly dashed lines indicate 95% prediction intervals. (‡): Correlation at significance level of $P<0.01$. CP equivalent: chlorpromazine equivalent, 95%CI: 95% confidence interval, 95%PI: 95% prediction interval.

participants in these studies also differed from that of the present study in that both genders were included. Furthermore, MDD patients in the study by Pitts et al (1995) all scored 18 or above on the HAMD-17, while the MDD patients in the present study included those in a remitted state. These differences in composition of study samples should be carefully considered when comparing findings across studies.

Some limitations must be considered when interpreting the results of this study. First, the effects of medication could not be fully controlled due to the variability in types and doses. Future studies should examine oxytocin levels in untreated patients to elucidate the role of oxytocin in the pathophysiology of schizophrenia and depression. Treatment duration may also affect oxytocin levels. However, since all of the schizophrenic patients that were prescribed antipsychotics were on chronic treatment with the medication, treatment duration is unlikely to have confounded the main findings of the present study. Secondly, as mentioned above, the cross-sectional design did not allow for any definitive conclusions regarding the causal relationship between the CSF oxytocin levels, psychotropic medication, and symptom severity. Thirdly, only male participants were included in the present study. Previous studies suggest that effects of peripheral and intranasal oxytocin may differ between men and women (Domes et al., 2010; Rubin et al., 2010, 2011). Therefore, the present findings cannot be generalized to women. Finally, the risk of type II error was high due to the small sample size. The sample size in the present study was comparable to those of the previous studies that examined CSF oxytocin levels in patients with schizophrenia and depression (Beckmann et al., 1985; Glovinsky et al., 1994; Pitts et al., 1995). However, the power to detect a moderate difference (effect size of 0.50) in CSF oxytocin levels between patients and controls was relatively low (schizophrenia: 39%; MDD: 32%; calculated by G*Power 3.1.3 (Faul et al., 2007)). A larger sample may be necessary to detect small to moderate change in CSF oxytocin levels in psychiatric disorders.

In conclusion, we obtained no evidence of altered CSF oxytocin levels in patients with schizophrenia or those with MDD. However, lower CSF oxytocin levels may be related to higher SGA dose and more severe negative symptoms in schizophrenia, which is in line with the possibility that central oxytocin may ameliorate the severity of some symptoms of schizophrenia by improving social functioning.

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no role in the study design; the collection, analysis and interpretation of data, in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Daimei Sasayama and Kotaro Hattori designed the study. Daimei Sasayama, Kotaro Hattori, and Toshiya Teraishi performed the lumbar punctures. Daimei Sasayama, Kotaro Hattori, Toshiya Teraishi, Hiroaki Hori, Miho Ota, Sumiko Yoshida, Kunimasa Arima, and Hiroshi Kunugi screened and diagnosed the study participants. Daimei Sasayama wrote the draft of the manuscript. Hiroshi Kunugi supervised the writing of the paper. Teruhiko Higuchi and Naoji Amano gave critical comments on the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

The authors declare no conflicts of interest.

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症例報告

32歳で発症した舞踏病様不随意運動を伴う前頭側頭型認知症の一例

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抄録

筆者らは，32歳で発症し両下肢に舞踏病様の不随意運動を伴った前頭側頭型認知症（frontotemporal dementia；FTD）の1例を経験した．症例は38歳女性．統合失調症の家族歴あり．中国で生活をしていた32歳時，情動変化，家事遂行困難で発症し，反復言語，周徊，貧乏揺すり，脱抑制的行動が出現して，現地で入院となった．画像検査で前頭側頭葉変性症と診断され，入院継続のためX年に帰国，当院に入院となった．MRIで両側前頭・側頭葉に強い萎縮，脳血流SPECTで同部位に血流低下を認めた．両下肢の舞踏病様不随意運動および筋トーヌス低下を認めた．Huntingtin遺伝子等の舞踏病をきたす遺伝性疾患の遺伝子，*TARDBP*，*GRN*，*FUS*等の前頭側頭葉変性症に関連する遺伝子を調べたが，検索し得た範囲では異常は同定されなかった．本例は，若年発症である点，内因性精神疾患（統合失調症）の家族負因を有している点，舞踏病様不随意運動を呈した点で特異であった．

Key words：前頭側頭葉変性症，前頭側頭型認知症，若年発症，舞踏病様不随運動

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はじめに

前頭側頭葉変性症（frontotemporal lobar degeneration；FTLD）は初老期に発症する認知症疾患の約20%を占める疾患群[19]である．臨床的には発病早期に冒される脳領域に応じて，前頭側頭型認知症（frontotemporal dementia；FTD），進行性非流暢性失語（progressive non-fluent aphasia；PNFA），意味性認知症（semantic dementia；SD）に分類されている[15]．FTLDの85%前後は40～60歳代に発症するとされ[7,11]，20～30歳代での発症はまれである[3,5,10,14,20~22]．今回筆者らは，32歳で発症したFTDの1例を経験したので報告する．本例は，統合失調症の家族歴を有し，両下肢に舞踏病様不随意運動を伴っていた点が特異であった．FTLDは臨床的，病理学的，遺伝学的に多様な疾患群であり，本症例の病像は同疾患群を考察するうえで重要な示唆を与えるものと考えられる．

なお症例呈示に際しては，個人情報保護のため，本報告の趣旨に影響を与えない範囲で若干の改変を加え，家族からの承諾を得ている．

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Ⅰ．症　例

〈症例〉38歳，女性

● 家族歴

父親がアルコール依存症，弟，母方叔母のおの

おの１人に統合失調症の罹患者がいる．

● 既往歴

特記事項なし．

● 生活歴

右利き．成長発達に遅れなし．高校卒業後，20歳で中国の大学に進学し，留学生として同国で生活をしていた．

● 現病歴

X-4年（32歳），急に泣き出す等の感情失禁が出現し，意欲低下から自宅に閉居しがちとなった．X-2年（34歳），身なりに無頓着となり，「行こう行こう」等の反復言語，周徊，貧乏揺すり，麺類をはじめとする炭水化物の過食が出現した．万引きのため警察に逮捕されることも数回あったが，無反省で平然としていた．友人に連れられ，中国の病院を受診し，うつ病と診断された．その後不安焦燥が悪化し，常同的に家の中を歩き続ける周徊が目立つようになり，X-1年（35歳），同国の病院へ入院となった．フルボキサミン（fluvoxamine），オランザピン（olanzapine）等による薬物療法や修正型電気けいれん療法が施行されたが，いずれも奏効しなかった．頭部MRIにてFTLDが疑われ，メマンチン（memantine）10 mg/日が開始されたが，効果はみられなかった．髄液検査では14-3-3タンパクは陰性であった．X年（36歳），帰国し，大使館経由で当院に入院となった．

● 入院時現症

無表情だが，顔面をしかめる，舌を突き出す，下肢を粗大に不規則に動かす等の舞踏病様の不随意運動を認めた．落ち着きなく手をぱちぱちと叩き，膝を擦るといった動作を繰り返し（反復行動），注意は保持できず，無関心，考え不精，立ち去り行動等を認め，我が道を行く行動も目立った．神経学的診察では，軽度の筋トーヌス低下を認めたが，深部腱反射は正常，眼球運動障害，舌や骨間筋の萎縮，筋線維束攣縮，原始反射，小脳失調，構音障害，嚥下障害，感覚障害等は認めなかった．入院の時点では言語理解や相貌認知は良好であった．頭部MRIにて両側前頭葉・側頭葉の前部に限局した高度の萎縮，両側側脳室前角高度拡大，尾状核の萎縮を認めた（図1a）．脳血流SPECTでは萎縮部位に一致した血流低下を認めた（図2）．改訂長谷川式簡易知能評価スケール（HDS-R）14点（遅延再生0/6），Mini-Mental State Examination（MMSE）18点（同0/3）であり，血液検査では有棘赤血球は認めず，βリポタンパクは327 mb/dlと正常であり，髄液中総タウタンパク（157 pg/ml），リン酸化タウ（22.7 pg/ml）も正常であった．ウェクスラー成人知能検査改訂版（Wechsler Adult Intelligence Scale-Revised；WAIS-R）は施行困難であった．筋電図では，脱神経電位は認めなかった．

● 遺伝子検索

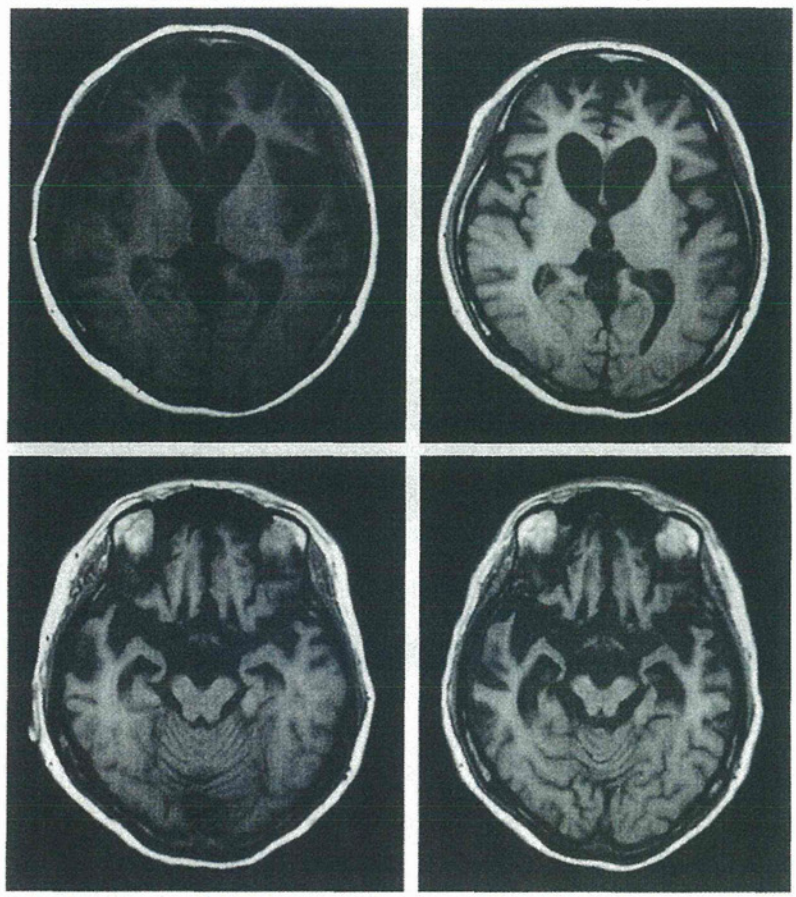
本例は若年発症であること，舞踏病様不随意運動を伴っていること，統合失調症の家族歴があること等から，遺伝性の疾患である可能性を考え，家族の同意を得たうえで以下の遺伝子について検索を行った：microtubule-associated protein tau（*MAPT*），fused in sarcoma（*FUS*），TAR DNA-binding protein 43（*TARDBP*），progranulin（*GRN*），presenilin-1（*PSEN1*），presenilin-2（*PSEN2*），amyloid precursor protein（*APP*），Huntingtin（*HTT*），脊髄小脳変性症SCA-17原因遺伝子（TATA-box-binding protein；*TBP*），歯状核赤核淡蒼球ルイ体萎縮症（dentatorubral-pallidoluysian atrophy；DRPLA）原因遺伝子（atrophin-1；*ATN1*），有棘赤血球舞踏病原因遺伝子（vacuolar protein sorting 13 homolog A；*VPS13A*），McLeod症候群原因遺伝子（membrane transport protein XK；*XK*），neurodegeneration with brain iron accumulation（NBIA）原因遺伝子のひとつである85 kDa calcium-independent phospholipase A2（*PLA2G6*）．

しかし，これらの遺伝子に異常は認められなかった．

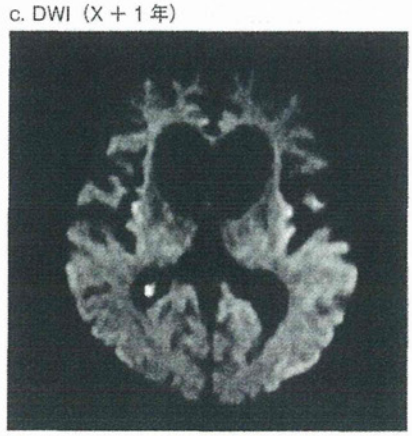
● 経過

メマンチンは当時国内未発売であったため中止され，ドネペジル（donepezil）が開始されたが，5 mg/日に増量した時点で尿失禁が出現し，中止された．病棟内を落ち着きなく徘徊し，窓やカー

a. T_1 強調画像（入院時，X年）　b. T_1 強調画像（X＋1年）

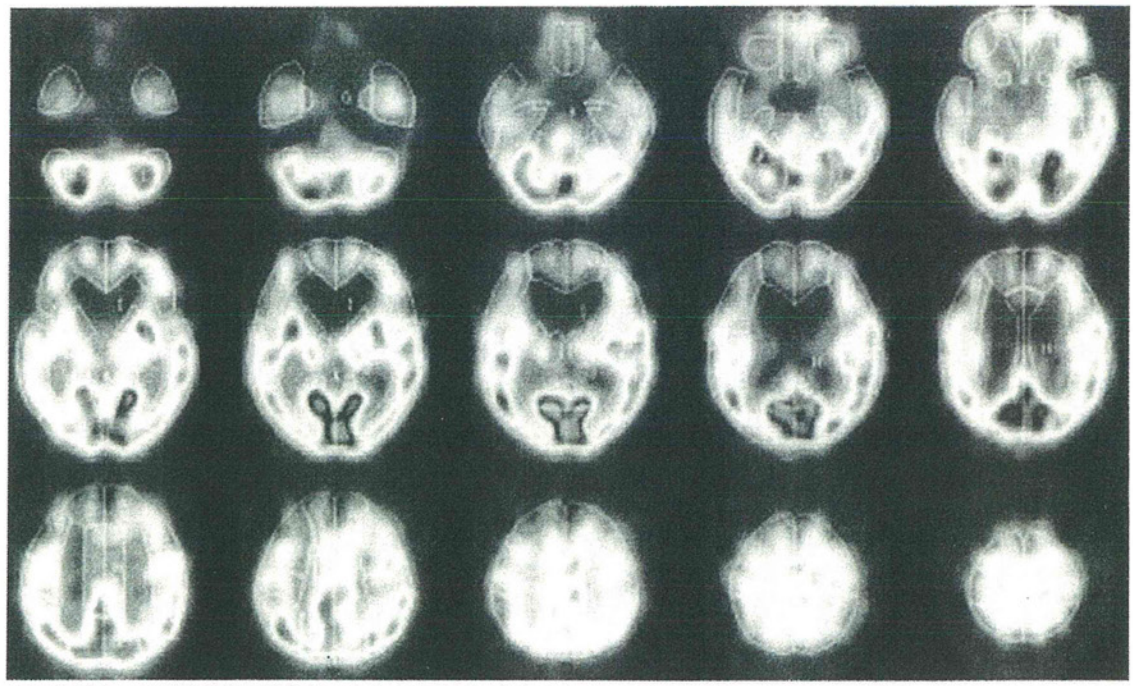


c. DWI（X＋1年）



a，b：入院時，両側前頭葉・側頭葉の前部に限局した高度の萎縮，側脳室前角高度拡大，尾状核萎縮を認めた．1年後，さらに萎縮は進行し，第三・第四脳室の拡大，中脳，橋，延髄等の脳幹部の萎縮も認めた．
c：大脳皮質，基底核，視床の高信号は認めなかった．

図1　頭部MRI（T_1 強調画像および拡散強調画像〈DWI〉）



両側前頭葉，側頭葉前部，尾状核に有意な血流低下を認めた．

図2　脳血流 SPECT（^{99m}Tc-ECD，入院時，X年）

テンをすべて開けて回る，黄色の物を触って回る等の強迫的・儀式的行動が顕在化した．同年12月には自発言語はほぼ消失し，指をしゃぶる等の口唇傾向，盗食，不潔行動が散見されるようになり，人格水準低下はさらに進行した．このころより，男性患者のベッドに入り込む等，脱抑制的行動が活発化し，相貌認知の障害も出現したが，知覚・運動機能，視空間認知機能，手続き記憶は保たれていた．X＋1年，両足を擦り合わせるアテトーゼ様の不随意運動を認めるものの，粗大な不随意運動は消失し，深部腱反射は亢進し，口尖らし反射，吸引反射，把握反射等の原始反射が陽性となった．同時期施行の頭部MRIでは両側前頭・側頭葉前部の高度の萎縮，側脳室拡大に加え，第三・第四脳室も拡大，中脳，橋，延髄等の脳幹部の萎縮も認めた（図1b）．拡散強調画像では大脳皮質，基底核，視床の高信号は認めなかった（図1c）．X＋2年，歩行困難となり，口唇の自傷行為や嚥下機能低下が出現した．現在，足関節の内転と外転を緩やかに繰り返す不随意運動は持続し，寝たきりの状態で経過している．

Ⅱ．考　察

本例は，32歳で発症し，自発性低下，感情失禁，反復言語，周徊，炭水化物の過食，万引き，立ち去り行動，強迫的・儀式的行動，進行性の失語，口唇傾向，盗食，不潔行動等の臨床症状を認め，FTLDの臨床的診断基準[15]を満たしていた．画像所見は，やや右側優位の前頭葉，側頭葉前部の高度萎縮を示し，同部位の血流低下を認めた．言語障害の特徴として，入院初期から発話量が少なく，発話内容の簡素化がみられ，運動性失語の像を呈していた．発話自体は比較的流暢で文法，構音，復唱の障害や，錯語，錯読は認めず，また，鉛筆を見て「エンピツ」と答え，スラスラと漫画を描く等，語想起や言語理解の障害はなく，意味記憶障害も認めず，PNFAやSDとは言い難かった．以上から，臨床診断はFTDとした．

鑑別診断として，近年報告された病初期から前頭葉症状が目立つアルツハイマー病（frontal