The disagreement in functional brain imaging studies might be attributed to participant's age, task demands or the experimental paradigm, such as event-related design or blocked design. Since few studies included participants with a broad range in age from childhood to adulthood, it is unclear whether the developmental change occurs between adolescence and adulthood and when it achieves its peak. Moreover, although previous studies have investigated the anterior frontal region, that is, the frontopolar regions (BA9/10), they have not focused on it. The frontopolar regions have a higher-order integrative prefrontal function [16] and comparative studies of humans and apes [17] suggested that they have enlarged and become specialized during hominid evolution. The frontopolar regions might coordinate VLPFC and DLPFC functions in order to achieve task goals or maximize task performance [18–20], and might evaluate internally generated information [21]. Because the frontopolar cortex is located in the vicinity of air-filled spaces of the nasal cavity, the corresponding magnetic susceptibility differences at air–tissue or bone–tissue interfaces result in severe distortions and regional signal losses in long-TE gradient-echo images, particularly for ultrafast imaging techniques such as echo-planar imaging in a high magnetic field. Therefore, such observation without signal losses in the frontopolar PFC might be one of the reasons for the superiority of NIRS.

NIRS is one of the most promising noninvasive functional neuroimaging tools to allow comparative evaluation of cortical hemodynamic response for children and individuals with psychiatric disorders. NIRS can measure the signals reflecting relative concentrations change of oxy-hemoglobin (Δoxy-Hb) and deoxy-hemoglobin (Δdeoxy-Hb), which are assumed to reflect regional cerebral blood volume (rCBV). While fMRI and PET have an excellent spatial resolution, they are limited in that they require a large apparatuse that prevents their use in bedside settings for diagnostic and treatment purposes. In contrast, NIRS is a neuroimaging modality that, for the following reasons is especially suitable for assessing the PFC of infants [22], children [14,15] and psychiatric disorders [23–28] because NIRS is relatively insensitive to motion artifacts, it can be applied to experiments that might cause some motion of the subjects, such as vocalization. Second, the subject can be examined in a natural sitting position, without any surrounding distraction. Third, the cost is much lower than other neuroimaging modalities and the set-up is very easy. Fourth, as the test-retest reliability at weekly and monthly intervals has demonstrated [29,30], NIRS can be applied to longitudinal assessment following intervention. Fifth, the high temporal resolution of NIRS is useful in characterizing the time course of prefrontal activity [23–25].

By simultaneous measurements with other methodologies, it has been shown that the Δoxy-Hb measured by NIRS correlates with the rCBF change in 15H2O PET [31] and the blood oxygenation level-dependent [32] signal in fMRI [33]. In other fMRI studies [32,34,35], in which the Δoxy-Hb was not analyzed, the Δdeoxy-Hb in NIRS has been correlated with the BOLD signal.

Moreover, previous studies showed that the verbal fluency test is a valid cognitive activation task to evaluate ΔHb in PFC using NIRS [24–26,28,31]. In NIRS studies recording the ΔHb during several tasks for the same subject group, the smaller-than-normal Δoxy-Hb during the cognitive tasks involving primarily the PFC, such as the letter fluency test and the random number generation task, was task specific in schizophrenia, i.e., this was not evident during other tasks, such as the sequential finger-to-thumb task [36], or the finger tapping task [24]. These findings suggested that the Δoxy-Hb reflected the neural activation but not general or nonspecific factors, such as impaired vascular responsiveness irrespective of neural activation or optical pathlength.

Thus, the present study investigated the developmental change in frontopolar PFC activation associated with the letter fluency task by using NIRS, in a group of subjects that included preschool children to adults.

Methods

1) Subjects

Subjects were 48 typically-developing children and adolescents (22 male and 26 female; age range, 5–18 years; mean age, 10.9; mean IQ, 106.2) and 22 healthy adults (11 male and 11 female; age range, 21–37 years; mean age, 27.3; mean IQ, 113.1) (Table 1). Participants were mainly recruited from college students, hospital staff, their acquaintances and children, and those who volunteered for participating through the laboratory's web site. When siblings or twin pairs participated in this study, only one was randomly selected and included in the data analysis (five children were from siblings and 23 children from twin pairs). As shown in the results section, the twin subjects and non-twin subjects did not significantly differ in ΔHb. The exclusion criteria were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 minutes, a history of electroconvulsive therapy, and alcohol/substance abuse or addiction. An additional exclusion criterion was a history of psychiatric disease or a family history of axis I disorder in their first-degree relatives. IQs were evaluated with the WISC-III or WAIS-R. All participants were right-handed as based on the Edinburgh Inventory [37] and were native Japanese speakers.

2) Ethics

The ethical committee of the Faculty of Medicine, University of Tokyo approved this study (No. 630-5). All adult participants gave written informed consent. All child participants gave informed assent and their parents gave written informed consent.

3) Activation task

The activation task consisted of a 30 sec rest, a 30 sec letter fluency task and a 30 sec rest. In the letter fluency task, participants were asked to say as many words that began with a Japanese character /a/ as they could. The participants sat on a chair with their eyes open and held their hands on their lap throughout the measurement. The auditory cues were presented at the start and end of the letter fluency task or rest. Hemoglobin concentration changes were measured during the activation task. The activation task was similar to that in previous studies [24,26], but 3 changes were introduced to make the task suitable for children: 1) In the pre- and post-task participants were silent

Table 1. Mean of age and IQ in each group.

	Child/ adolescent		Adult	
	Male	Female	Male	Female
n	22	26	11	11
age	9.9±2.7	11.7±3.8	26.5±5.7	28.2±5.5
(range)	(5.8~17.1)	(5.5~18.6)	(21.4~37.4)	(21.8~36.4)
IQ[a]	108.5±13.5	104.2±11.0	115.9±11.4	110.4±10.1
(range)	(81~137)	(82~123)	(94~128)	(92~125)

[a]For participants aged 15 and under IQ was evaluated with the WISC-III, for participants aged 16 and over it was estimated by four subtests of the WAIS-R.

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instead of repeating moras; 2) The time period of the letter fluency task and post-task was shortened to 30 sec from 60 sec; 3) Only a single mora was used in the letter fluency task. The number of words generated during the letter fluency task was determined as a measure of task performance.

4) NIRS measurement

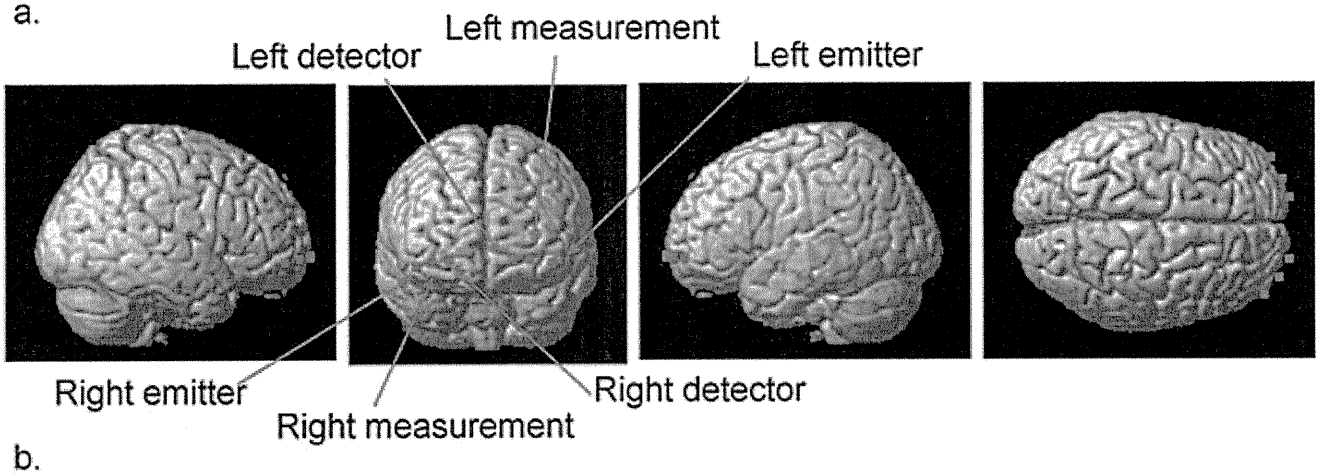
Δoxy-Hb and Δdeoxy-Hb was measured using a 2-channel NIRS machine (NIRO200, Hamamatsu Photonics, Inc) at three wavelengths of near-infrared light (775, 810, 850 nm). The measurement principles were based on the modified Beer-Lambert law, which calculates Δoxy-Hb and Δdeoxy-Hb from the light attenuation change at a given measured point. Δoxy-Hb and Δdeoxy-Hb values include a differential pathlength factor and are given in units of mMmm. Each of the two probes consisted of an emitter and a detector separated by 4 cm. The two NIRS probes were placed on the subject's prefrontal regions and secured using double-sided adhesive tape such that the detectors were positioned at Fp1 and Fp2 with the emitters positioned 4 cm on the lateral side of the detectors along the T3–T4 line, according to the international 10/20 system. The machine measured ΔHb approximately 2–3 cm beneath the scalp, i.e., the cortical surface area [31,34]. NIRS probes measured oxygenation at the Brodmann's area 10 (figure 1). The correspondence of the probe positions and the measurement areas on the cerebral cortex was confirmed by superimposing the measurement positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex for a healthy adult. The locations of NIRO probe were probabilistically estimated and anatomically labeled in the standard brain space (Brodmann's Area) according to [38]. Also, the correspondence was supported by a multisubject study of anatomical cranio-cerebral correction via the international 10–20 system [39]. The sampling time for the recording was 0.5 sec. Baseline correction was made by using the average ΔHb value during the first 30 sec rest, and then the average ΔHb value during the 30 sec task period was calculated in each hemisphere.

5) Statistical Analysis

A 2-way ANOVA with age (child/adolescent, adult) and gender (male, female) as the between-subjects factors used to analyze task performance.

For the mean ΔHb during the 30 sec task period, a 3-way ANCOVA was performed with age (child/adolescent, adult) and gender (male, female) as the between-subjects factors, hemisphere (left, right) as the within-subjects factor and task performance as a covariate. When the sphericity assumption was violated, Green-

a.



b.

Probe	X	Y	Z	Brodman Area(Talairach Daemon)	Percentage
R detector	24	71	-4	10 – Frontopolar area	0.861
				11 – Orbitofrontal area	0.139
R measurment	36	66	-6	10 – Frontopolar area	0.775
				11 – Orbitofrontal area	0.225
R emitter	46	57	-7	10 – Frontopolar area	0.579
				11 – Orbitofrontal area	0.289
				47 – Inferior prefrontal gyrus	0.132
L detector	-15	72	-4	10 – Frontopolar area	0.770
				11 – Orbitofrontal area	0.230
L measurement	-28	68	-4	10 – Frontopolar area	0.881
				11 – Orbitofrontal area	0.119
L emitter	-41	60	-6	10 – Frontopolar area	0.733
				11 – Orbitofrontal area	0.255
				47 – Inferior prefrontal gyrus	0.012

Figure 1. The probe positions and the measurement areas. a:The correspondence of the probe positions and the measurement areas on the cerebral cortex. b: The locations of NIRO probe were probabilistically estimated and anatomically labeled in the standard brain space (Brodmann's Area) according to [39].
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house-Geisser correction was applied and the associated epsilon was reported. For post-hoc analysis, the mean ΔHb of the hemispheres was used as the dependent variable with task performance as a covariate and statistically significant level was defined as $p<.025$ (Bonferroni correction).

We calculated the Pearson's correlation between the average ΔHb and task performance and age separately for each gender in the child/adolescent and adult groups. Second, the comparison of correlation coefficients between male and female was performed.

Results

1) Task performance

The mean number of words generated during the letter fluency task was: 4.32 (SD = 2.61) for male; 4.38 (SD = 2.23) for female in the child/adolescent group, and 9.27 (SD = 2.90) for male; 8.55 (SD = 1.51) for female in the adult group. A main effect of age was significant ($F(1,66) = 55.20$, $p<.001$), but the effect of gender and the interaction were not significant (gender: $F(1,66) = .29$, $p = .59$; interaction gender and age: $F(1,66) = .42$, $p = .52$).

2) Group comparisons of the ΔHb

Twenty-three of the participants in the child/adolescent group were one of a pair of twins. T-test showed that the mean ΔHb was not significantly different between non-twin and twin subject in the child/adolescent group (oxy-Hb: $t(46) = .48$, $p = .63$; deoxy-Hb: $t(46) = -.90$, $p = .37$), indicating that including one of twins may not have significantly influenced the conclusions of the study.

Figure 2 shows grand average waveforms of hemoglobin concentration changes for each group. The average Δoxy-Hb in the right hemisphere was: mean 0.15 (SD = 0.36) for male; 0.30 (SD = 0.30) for female in the child/adolescent group and 0.65 (SD = 0.45) for male; 0.13 (SD = 0.20) for female in the adult group, and that in the left hemisphere was: mean 0.12 (SD = 0.44) for male; 0.26 (SD = 0.29) for female in the child/adolescent group and 0.57 (SD = 0.49) for male; 0.17 (SD = 0.11) for female in the adult group. For the Δoxy-Hb, there was a significant interaction between age and gender ($F(1,65) = 12.27$, $p<.001$). All main effects and other interactions were not significant (age: $F(1, 65) = 3.69$, $p = .059$; gender: $F(1,65) = 3.54$, $p = .07$; hemisphere: $F(1,65) = 1.13$, $p = .29$; interactions of age and hemisphere: $F(1,65) = 1.64$, $p = .21$, gender and hemisphere: $F(1,65) = 0.97$, $p = .33$, age, gender and hemisphere: $F(1,65) = 1.00$, $p = .32$).

Since we found a significant interaction between age and gender, we next conducted post-hoc analyses in two ways using the mean Δoxy-Hb of the hemispheres as the dependent variable with task performance as a covariate (Figure 3). First, we compared Δoxy-Hb two age groups separately for each gender. For male, the average Δoxy-Hb in the adult group was significantly larger than that in the child/adolescent group ($F(1,30) = 11.55$, $p<.01$). For female, however, it did not reach at a significant level ($F(1,34) = 4.69$, $p = .04$). Second, we compared Δoxy-Hb between two gender groups separately for each age group. For the child/adolescent group, there was not a significant difference ($F(1,45) = 2.01$, $p = .16$), but in the adult group the average Δoxy-Hb in male was significantly larger than that in female ($F(1,19) = 16.15$, $p<.01$).

The average Δdeoxy-Hb in the right hemisphere was mean −.02 (SD = .08) in the child/adolescent group, −.05 (SD = .13) in the adult group, and in the left hemisphere was mean −.03 (SD = .10) in the child/adolescent group, and −.05 (SD = .11) in the adult group. For the Δdeoxy-Hb, there was a significant main effect of hemisphere ($F(1,65) = .4.40$, $p = .04$). There were no other significant main effects and any interactions (age: $F(1,65) = .57$, $p = .46$; gender: $F(1,65) = 1.48$, $p = .23$; interactions of age and gender ($F(1,65) = 1.54$, $p = .22$, age and hemisphere: $F(1,65) = 2.64$, $p = .11$, gender and hemisphere: $F(1,65) = .17$, $p = .69$, age, gender and hemisphere: $F(1,65) = 2.69$, $p = .11$).

3) Correlation analysis

Since hemoglobin concentrations of both hemispheres did not behave differently as indicated by a lack of significant interactions with hemisphere in the main ANCOVA, we used the mean ΔHb of the hemispheres for the correlational analyses. The the child/adolescent group showed a strongly positive correlation between Δoxy-Hb and age (male: $r = 0.50$, $p = .017$; female: $r = .67$, $p<.001$), whereas the adult group showed a weak negative correlation which did not reach a significant level (male: $r = -.15$, $p = .65$; female: $r = -.37$, $p = .27$) (Figure 4). The difference in correlation coefficients between male and female was not significant in the child/adolescent or adult groups (Fisher's r to z transformation; child/adolescent, $z = -.76$, $p = .45$; adult, $z = .47$, $p = .64$). There were no correlations between the Δoxy-Hb and task performance in the child/adolescent (male: $r = -.07$, $p = .75$; female: $r = .30$, $p = .14$) or adult groups (male: $r = -.59$, $p = .06$; female: $r = .05$, $p = .90$).

The Δdeoxy-Hb were not correlated with age in the child/adolescent group (male: $r = -.11$, $p = .62$; female: $r = -.04$, $p = .85$), or in the adult group (male: $r = -.28$, $p = .41$; female: $r = -.41$, $p = .21$). The difference in correlation coefficients

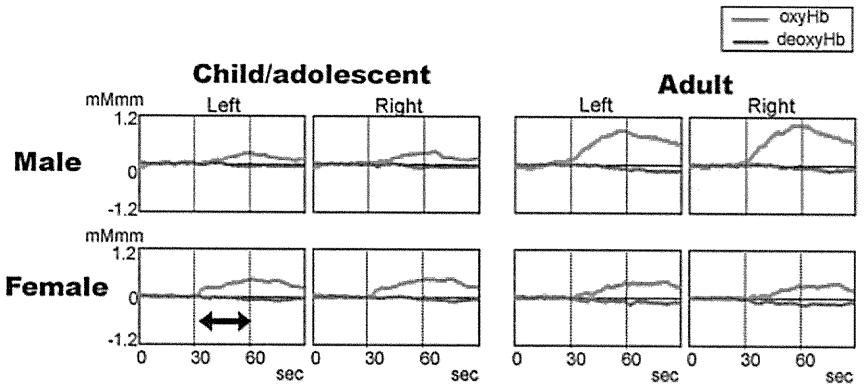

Figure 2. Grand average waveforms of ΔHb during the letter fluency task. Upper: male, lower: female, right: adult group, left: child/adolescent group. Line: red, oxyhemoglobin; blue, deoxyhemoglobin. The period of the activation task is between the two dotted lines.
doi:10.1371/journal.pone.0025944.g002

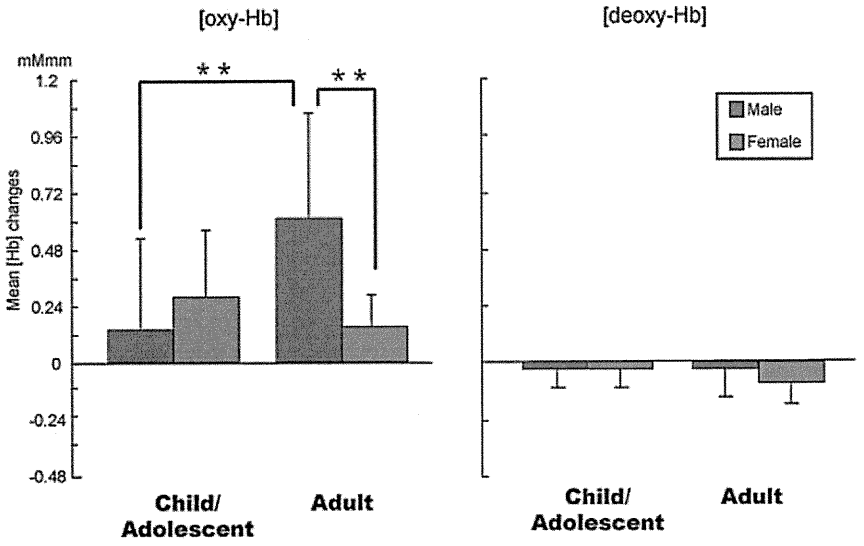

Figure 3. The mean ΔHb of the hemispheres in each group. Left: Δoxy-Hb, right: Δdeoxy-Hb, blue: male, red: female. The average Δoxy-Hb in the adult group was significantly larger than that in the child/adolescent group for male ($F(1,30) = 11.55$, $p<.01$). Moreover, for the adult group the average Δoxy-Hb in male was significantly larger than that in female ($F(1,19) = 16.15$, $p<.01$).
doi:10.1371/journal.pone.0025944.g003

between male and female was not significant in the child/adolescent or adult groups (child/adolescent, $z = .23$, $p = .82$; adult, $z = .31$, $p = .76$). There were no correlations between the Δdeoxy-Hb and task performance in the child/adolescent (male: $r = -.02$, $p = .94$; female: $r = .01$, $p = .95$) or adult groups (male: $r = -.19$, $p = .57$; female: $r = .31$, $p = .35$).

Discussion

To our knowledge, this is the first report of developmental changes in frontopolar PFC hemodynamic data from preschool children to adults. First, in the children/adolescent group the Δoxy-Hb during the verbal fluency task was significantly increased with age. Contrary to the strongly positive correlation between prefrontal activation and age in the child/adolescent group, the correlation coefficient was slightly negative but not statistically significant in the adult group. Second, the effect of gender on Δoxy-Hb differed depending on age, where in the adult group the males showed a larger Δoxy-Hb than the females, but in the child/adolescent group there was no difference between the males and the females.

1) Developmental change of the frontopolar PFC

Meta-analysis of fMRI [40] and previous multi-channel NIRS studies [24–26,28] showed that frontopolar areas were not the sites of typical activation during letter fluency task, but that widespread regions of the prefrontal cortical surface area and superior temporal regions were recruited. However, comparative studies of humans and apes showed that the frontopolar regions have enlarged and become specialized during hominid evolution [17]. Previous NIRS studies, furthermore, found that the activation of frontpolar region during the letter fluency test were associated with the social functioning in schizophrenia [28]. Thus, even if the frontpolar region was not mainly recruited during the letter fluency test, the activation of this area has important roles of human life because the frontopolar regions have a higher-order integrative prefrontal function [16]. In this study, frontpolar activation increased with age and boys showed smaller activation than men. Although an fMRI study using the verbal fluency task found that activation of the ventrolateral prefrontal cortex (BA44/45) is larger in children than in adults [13], it is not necessarily contradictory that the time course does not agree with previous

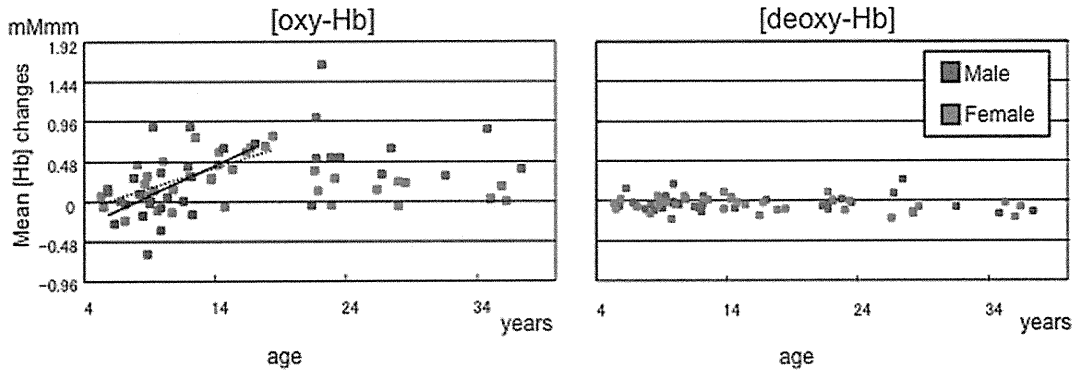

Figure 4. The scatter plots of age and the mean ΔHb of the hemispheres. Left: Δoxy-Hb, right: Δdeoxy-Hb, blue: male, red: female. Contrary to the strongly positive correlation between Δoxy-Hb and age in the child/adolescent group (male: $r = 0.50$, $p = .017$; female: $r = .67$, $p<.001$), the correlation coefficient was slightly negative but not statistically significant in the adult group.
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developmental studies on the function at other regions of the prefrontal cortex. Rather, the present NIRS data was consistent in showing that the BA10 is developed latest in the ontogenetic change and might suggest that the cortical area recruited by the verbal fluency task might shift from the dorso-ventrolateral to the anterior polar region with age. However, this interpretation should be validated in future studies using an instrument with a wider coverage of prefrontal and temporal area.

The results of the correlation analysis in the child/adolescent group suggest that recruitment of the frontopolar PFC during letter fluency tasks increases with age in childhood and adolescence, and that development appears to continue into late adolescence. These results are in agreement with a previous morphological study on the frontopolar PFC [41].

Contrary to the strongly positive correlation between prefrontal activation and age in the child/adolescent group, the correlation coefficient was slightly negative but not statistically significant in the adult group. This was consistent with previous NIRS studies using the letter fluency task, in which the Δoxy-Hb in middle age was smaller than that in young adults [42,43]. A failure in reaching statistically significant level in this study may be due to the narrow range of the participant's age and the small sample size in the adult group.

2) Gender effect on frontopolar PFC activation

In the adult group, the mean Δoxy-Hb during the letter fluency test was larger in the males than in the females. This finding of gender effect on Δoxy-Hb was in agreement with a previous NIRS study using the same task [25]. Mean IQ and mean age were not likely to be main confounding factors, since they were not different between genders.

The gender effect on Δoxy-Hb differed depending on age, where in the child/adolescent group there were no significant differences in correlation coefficients or mean Δoxy-Hb between genders. This developmental course was compatible with other morphological data that reported no gender difference in the fronopolar thickness in subjects 8–20 years of age [41]. In comparison of Δoxy-Hb between the two age groups separately for each gender, the males showed a larger Δoxy-Hb in the adult goup than in the child/adolescent group, but the females showed no difference between the two age groups. Taken together, these results suggested that the developmental change in the frontopolar PFC hemodynamic response until late adolescence occurred independent of gender and that the peak of the Δoxy-Hb was younger and smaller in females than in males. Those findings could be related to a high plateau peak of frontal gray matter at younger and smaller in females than in males [4].

3) Methodological issues

First, we used the resting state as the baseline to facilitate applicability of the task for child participants, although we assumed a simple vocalization task for the baseline would be more ideal to derive a pure activation related to the letter fluency task. Therefore, the age-dependent increase in frontopolar PFC activation may reflect an age-dependent increase in brain activity due to vocalization per se or age-dependent hypoperfusion during the baseline period (resting state). PET studies have reported age-dependent decreased oxygen metabolism and regional cerebral blood flow (rCBF) during the resting state in the frontal areas [7,44]. Thus, it may be possible that the adolescents were hypoperfused during the baseline, and then activation during the task would have been larger compared with that for the younger children. However, this interpretation is incomplete because the age at peak Δoxy-Hb in this study was incongruent with a peak of the rCBF [44] and the glucose metabolic rate [7] in PET studies. Furthermore, it is impossible to distinguish whether these results were due to 'cognitive development' or just to 'phonation development' and 'structural development'. Thus, future studies should add a simple vocalization as the referential condition and investigate the structural development

Second, the design used in this study suffered from difference in optical properties of scalp and cortical tissues with age and gender. Adults are expected to have thicker skulls than children, and males' skulls are thicker than females'. Simulation studies on tissue optical properties [45] indicated that the thicker skull contributes toward decreasing amplitude of oxyHb signal. However, the current study showed that that the Δoxy-Hb was largest in the adult male. Thus, although individual difference in optical properties of scalp and cortical tissues is very important in theory, it may not have a substantial effect on the statistical conclusion reported here.

Third, as we measured activation of only the frontopolar regions of the PFC during a letter fluency test in this study, results could not be compared with the activation of other regions and tasks. Thus, a functional control task such as checkerboard rotation or finger tapping tasks and measurement of other regions as reference are needed to compensate individual difference in the tissue optical properties and provide more convincing results in future studies using a multi-channel NIRS machine.

Fourth, we used the cross-sectional design, not the longitudinal one. However, IQ was controlled between the child/adolescent and adult groups for each gender (male: $t(31) = -1.56$, $p = .13$; female: $t(35) = -1.58$, $p = .12$). Future research with a longitudinal design is necessary for a more comprehensive understanding of developmental change in the PFC.

Fifth, a recent NIRS study showed the influence of skin blood flow on NIRS signals measured on the forehead during a verbal fluency task [46]. This study criticized that frontopolar activation may not represent cortical change but non-cortical physiological signal, which is autonomic control. Thus, it remains possible that our data may at least partially represent the development of autonomic control. Future studies are needed to disentangle contribution of cerebral and skin blood flow on the NIRS signals in various NIRS apparatuses by using, for example, simultaneous measurement of NIRS and fMRI during cognitive activation.

4) Conclusion

The present study, which investigated frontopolar PFC activation during the verbal fluency test, suggested that functional development of the area continues to late adolescence. Although the developmental change of the frontopolar PFC was independent of gender from childhood to adolescence, in adulthood a gender difference was shown.

Acknowledgments

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Author Contributions

Conceived and designed the experiments: YK HK KK. Performed the experiments: YK TK RT HK AI-T. Analyzed the data: YK RT KK. Wrote the paper: YK KK.

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Sigma-1 Receptor Agonists as Therapeutic Drugs for Cognitive Impairment in Neuropsychiatric Diseases

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Abstract: Cognitive impairment is a core feature of patients with neuropsychiatric diseases such as schizophrenia and psychotic depression. The drugs currently used to treat cognitive impairment have significant limitations, ensuring that the search for more effective therapies remains active. Endoplasmic reticulum protein sigma-1 receptors are unique binding sites in the brain that exert a potent effect on multiple neurotransmitter systems. Accumulating evidence suggests that sigma-1 receptors play a role in both the pathophysiology of neuropsychiatric diseases, and the mechanistic action of some therapeutic drugs, such as the selective serotonin reuptake inhibitors (SSRIs), donepezil and neurosteroids. Among SSRIs, fluvoxamine, a potent sigma-1 receptor agonist, has the highest affinity at sigma-1 receptors. Sigma-1 receptor agonists greatly potentiate nerve-growth factor (NGF)-induced neurite outgrowth in PC12 cells, an effect that is antagonized by treatment with the selective sigma-1 receptor antagonist NE-100. Furthermore, phencyclidine (PCP)-induced cognitive impairment, associated with animal models of schizophrenia is significantly improved by sub-chronic administration of sigma-1 receptor agonists such as fluvoxamine, SA4503 (cutamesine) and donepezil. This effect is antagonized by co-administration of NE-100. A positron emission tomography (PET) study using the specific sigma-1 receptor ligand [^{11}C]SA4503 demonstrates that fluvoxamine and donepezil bind to sigma-1 receptors in the healthy human brain. In clinical studies, some sigma-1 receptor agonists, including fluvoxamine, donepezil and neurosteroids, improve cognitive impairment and clinical symptoms in neuropsychiatric diseases. In this article, we review the recent findings on sigma-1 receptor agonists as potential therapeutic drugs for the treatment of cognitive impairment in schizophrenia and psychotic depression.

Keywords: Sigma-1 receptor, Cognition, Schizophrenia, Psychotic depression, Delirium.

1. INTRODUCTION

Cognitive impairment is a common symptom in patients with neuropsychiatric disorders such as schizophrenia and major depressive disorder. Schizophrenia is characterized by three distinct symptom clusters: positive symptoms (*e.g.*, hallucinations and delusions), negative symptoms (*e.g.*, affective flattening, alogia and avolition), and cognitive impairment (*e.g.*, severe deterioration of working memory and attention). Cognitive impairment is a core feature of schizophrenia and its presence predicts both vocational and social disabilities for patients [1-4]. While positive symptoms are greatly improved with atypical antipsychotic medication, cognitive impairment is not greatly improved by therapy [5].

Cognitive impairment is also a ubiquitous and characteristic feature of major depressive disorder [6], often persisting despite otherwise effective antidepressant therapy. In addition, cognitive impairment can also be an adverse effect ("cognitive toxicity"), as a direct consequence of some antidepressant therapy [7]. The severity of major depression also has a bearing on the extent and magnitude of cognitive, psychomotor and memory impairment [8, 9]. Given the relative commonality of this disorder, and the lack of highly effective therapy, there is still a strong need for the development of pharmacological agents to improve cognitive impairment associated with neuropsychiatric disorders [10-14].

Sigma-1 receptors, discovered in 1976 by Martin and coworkers [15], were cloned in 1996 [16], and characterized as having an endoplasmic reticulum (ER) retention signal. Sigma-1 receptors on the ER regulate Ca^{2+} signaling *via* inositol 1,4,5-triphsphate (IP_3) receptors on the ER [17]. Interestingly, the ER protein sigma-1 receptors are Ca^{2+}-sensitive and are ligand-operated receptor chaperones at the mitochondrial associated ER membrane [18, 19]. The ER lumeral domain of the sigma-1 receptor possesses robust chaperone activity that prevents the aggregation of a variety of proteins *in vitro,* which stabilizes the ER Ca^{2+} channel IP_3 receptor *in vivo* [18, 20]. Sigma-1 receptors are predominantly expressed at the mitochondrial associated ER membrane, thereby regulating the IP_3 receptor-mediated Ca^{2+} influx from the ER to the mitochondria [18]. Sigma-1 receptors modulate ATP production and bioenergetics within cells [20].

Sigma-1 receptors regulate a number of neurotransmitter systems, including the glutamatergic, dopaminergic, serotonergic, noradrenergic, and cholinergic systems. Several lines of evidence implicate the role of sigma-1 receptors in the pathophysiology of neuropsychiatric disorders, such as mood disorders, anxiety disorders, and schizophrenia, and suggest that the receptor ligands may be potential therapeutic agents for these diseases [21-34]. This article reviews and discusses the role of sigma-1 receptor agonists as therapeutic agents, to improve cognitive impairment in neuropsychiatric disorders, particularly schizophrenia and major depressive disorder.

2. SIGMA-1 RECEPTOR AGONISTS AND NEUROPLASTICITY

Sigma-1 receptors play a role in synaptogenesis and myelination in the brain [35, 36], processes implicated in the pathology of schizophrenia [37-40] and depression [41, 39].

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) are widely used as therapeutic drugs for major depressive disorder. Although all SSRIs share the common function of the blockading serotonin transporters, leading to elevated serotonin levels throughout the central nervous system (CNS), it is well known that their secondary pharmacology is heterogeneous [42-44]. We have reported that some SSRIs possess high to moderate affinity for sigma-1, but not for sigma-2 receptors Table **1** [45]. *In vitro* experiments suggest that the affinity of SSRIs for sigma-1 receptors is as follows: fluvoxamine > sertraline >

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Table 1. ***In Vitro*** **Affinity of Various Antidepressants for Rat Sigma-1 Binding Sites (from Ref. [45])**

Drug	Ki (nM)		Ki ratio
SSRIs	**Sigma-1**	**Sigma-2**	**(Sigma-2/Sigma-1)**
Fluvoxamine	36	8,439	234
Sertraline	57	5,297	93
S(+)Fluoxetine	120	5,480	46
(±)Fluoxetine	240	16,100	68
Citalopram	292	5,410	19
Paroxetine	1,893	22,870	12
Tricyclic antidepressants			
Imipramine	343	2,107	6
Desipramine	1,987	11,430	6

fluoxetine > citalopram >> paroxetine. It is highly likely that some SSRIs such as fluvoxamine, utilize sigma-1 receptors in its mode of action [45].

Antidepressants are thought to exert their effect by inducing adaptive neuroplasticity such as neurite outgrowth [46-48, 30, 49]. The prototypic sigma-1 receptor agonist (+)-pentazocine, as well as the antidepressants imipramine and fluvoxamine, enhance nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells, in a concentration dependent manner [50]. The selective sigma-1 receptor antagonist, NE-100 [51], blocks these enhancements [50]. Recently, we reported that fluvoxamine, but not sertraline or paroxetine, significantly potentiates NGF-induced neurite outgrowth in PC12 cells, in a concentration dependent manner Fig. (**1**) [52]. Similarly, the sigma-1 receptor agonists, 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl) piperazine dihydrochloride (SA4503: cutamesine) [53], 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP) [54-56], dehydroepiandrosterone–sulfate (DHEA-S) [57, 58], and donepezil also potentiate NGF-induced outgrowth in PC12 cells, in a concentration-dependent manner [59, 52]. This outgrowth is greatly attenuated if NE-100 is co-administered Fig. (**1**) [59, 52]. All these findings suggest that sigma-1 receptors play an important role in NGF-induced neurite outgrowth, and that in the brain, selected antidepressants and compounds facilitate this neurite outgrowth, *via* sigma-1 receptors. However, the precise cellular and molecular mechanisms underlying these processes are not fully understood.

3. SIGMA-1 RECEPTOR AGONISTS AND COGNITION

Sigma-1 receptor agonists can improve acetylcholine (an anti-muscarinic drug)-related deficits in memory and cognition in rodent models [24, 25, 27, 60]. Selective receptor agonists, including igmesine and SA4503, reverse amnesia induced by muscarinic and nicotinic receptor antagonists [61, 62]. Furthermore, sigma-1 receptor agonists, such as (+)-SKF 10,047 and SA4503, release acetylcholine in the rat brain [63, 64]. Recently, methyl (1*R*,2*S*/1*S*,2*R*)-2-[4-hydroxy-4-phenylpiperidin-1-yl)methyl]-1-(4-methylphenyl) cyclopropanecarboxylate ((±)-PPCC) , a novel sigma-1 receptor agonist, has been shown to ameliorate cognitive impairment induced by selective cholinergic lesions in rats [65]. These findings suggest that sigma-1 receptor agonists can improve acetylcholine-related cognitive impairments through a mechanism of acetylcholine in the brain [27, 60].

Multiple lines of evidence suggest that aberrant glutamatergic neurotransmission *via* the *N*-methyl-D-aspartate (NMDA) receptors may precipitate the cognitive impairment associated with schizophrenia and major depression [66-71]. The NMDA receptor antagonists, such as phencyclidine (PCP), induce schizophrenia-like symptoms including cognitive impairment in healthy subjects [66]. As a consequence, the NMDA receptor antagonists, including PCP, are widely used to generate animal models of cognitive impairment. We have shown that PCP-induced cognitive impairment in a novel object recognition test is significantly improved by subsequent sub-chronic (2-week) administration of the atypical antipsychotic drug clozapine, but not the typical antipsychotic drug haloperidol [72]. Thus, the reversal of PCP-induced cognitive impairment as measured by the novel object recognition test, may be a potential animal model for atypical antipsychotic activity, in the amelioration of schizophrenia associated cognitive impairment [72]. Furthermore, we have found that repeated administration of PCP causes a significant reduction of sigma-1 receptors in the mouse hippocampus [73, 74], suggesting that a decrease in sigma-1 receptors may precipitate PCP-induced cognitive impairment.

4. POTENTIAL THERAPEUTIC DRUGS FOR COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

4.1. Fluvoxamine as a Sigma-1 Receptor Agonist

We have reported that PCP-induced cognitive impairment is significantly improved by subsequent sub-chronic (2-week) administration of fluvoxamine (20 mg/kg/day), but not paroxetine (10 mg/kg/day) [48] or sertraline (10 or 20 mg/kg/day) [73]. The effect of fluvoxamine on PCP-induced cognitive impairment is antagonized by co-administration of NE-100. Unlike fluvoxamine, sertraline which is an SSRI with a high affinity at sigma-1 receptors, does not attenuate PCP-induced cognitive deficits in mice. In addition, sertraline does not enhance NGF-induced neurite outgrowth in PC12 cells [52]. These findings suggest that fluvoxamine and sertraline may act as an agonist and an antagonist respectively, at sigma-1 receptors [52, 30, 73]. Also, it is likely that the agonistic activity of fluvoxamine at sigma-1 receptors mediates its therapeutic effect in PCP-induced cognitive impairment in mice.

4.2. Donepezil as a Sigma-1 Receptor Agonist

Donepezil is the most widely prescribed drug for Alzheimer's disease. It is thought to influence cognition and function by inhibiting acetylcholinesterase (AChE) in the brain, however, it has also been reported that donepezil binds sigma receptors in the brain [75]. This sigma-1 receptor binding is thought to promote the anti-depressive, anti-amnesic and neuroprotective effects of donepezil in

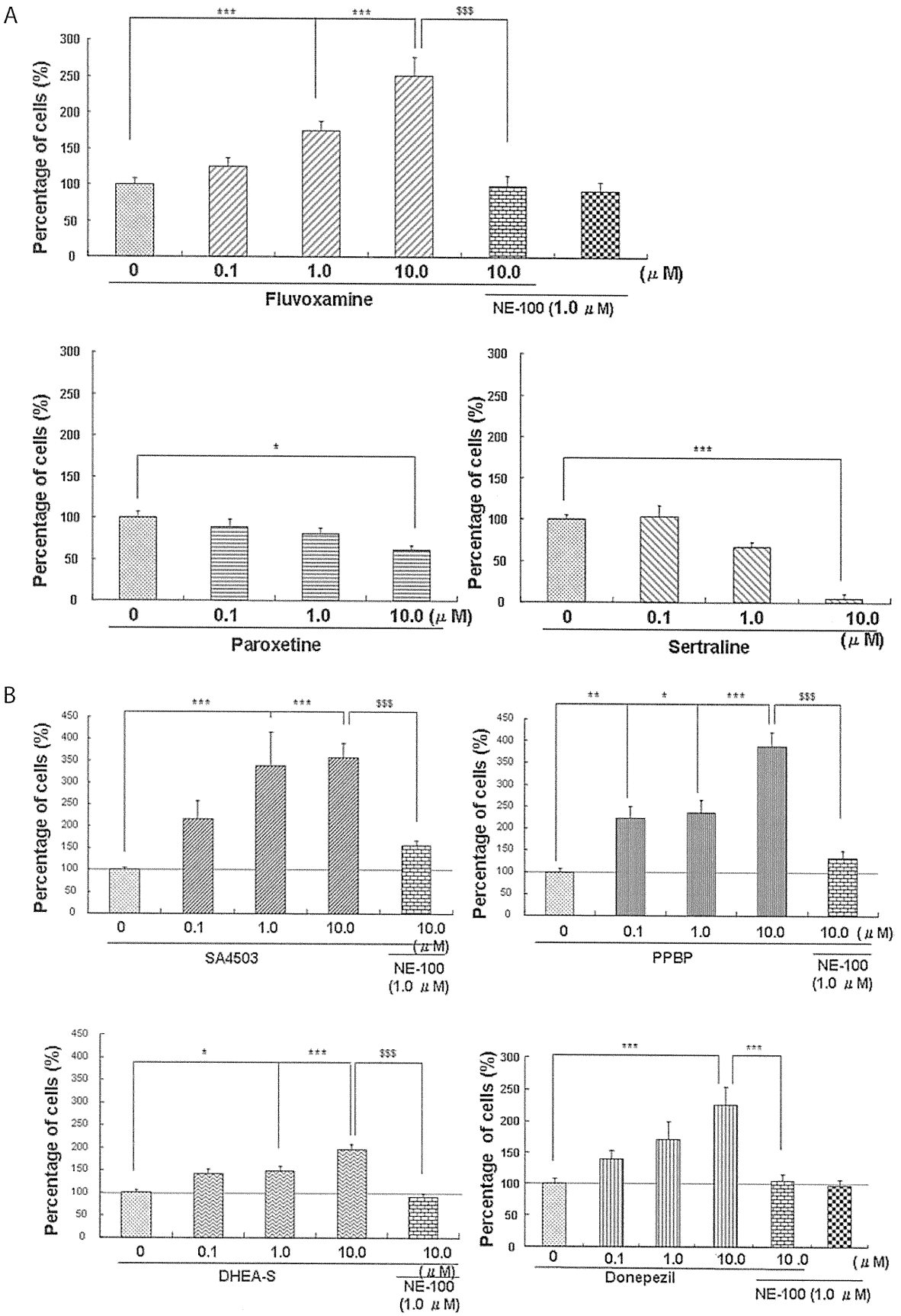

Fig. (1). Effects of SSRIs (fluvoxamine, paroxetine, sertraline) and sigma-1 receptor agonists (SA4503, PPBP, DHEA-S) on NGF-induced neurite outgrowth in PC12 cells. *P<0.05, **P<0.01, ***P<0.001 as compared with control (NGF alone) group. $^{\$\$\$}$P<0.001 as compared with drugs plus NE-100 group. The data are from Ref. [52] and Ref. [59].

the mouse forced swim test [76], and CO gas-induced [77] and amyloid $\beta_{25\text{-}35}$-induced neurotoxicity [78].

We have reported that PCP-induced cognitive impairment is significantly improved by subsequent, sub-chronic (2-week) administration of donepezil (1.0 mg/kg/day) [74]. This effect is antagonized by co-administration of the sigma-1 receptor antagonist NE-100. In contrast, PCP-induced cognitive impairment is not improved by subsequent, sub-chronic (2-week) administration of a different AChE inhibitor, physostigmine, that has no affinity to sigma-1 receptors [74]. These findings suggest that when treating mouse, PCP induced cognitive deficits, the therapeutic effect of donepezil is mediated *via* agonistic activity at sigma-1 receptors.

4.3. Neurosteroids as Sigma-1 Receptor Agonists

Neurosteroids, hormones produced in central and peripheral neurons, were first reported by Baulieu [79]. In the brain, concentrations of the neurosteroids, DHEA, DHEA-S, pregnenolone (PREG) and PREG-sulfate are far greater than in the circulatory system. Furthermore, concentrations in the brain remain high after adrenalectomy and orchiectomy, suggesting that these steroids do not originate from steroidogenic tissue but rather through local brain synthesis. As these neurosteroids do have moderate affinity towards sigma-1 receptors, they are considered endogenous ligands.

Neurosteroids may influence neuronal survival, neurite outgrowth and neurogenesis [80], as well as having varied effects on NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-aminobutyric acid type A ($GABA_A$), kainate, glycine, serotonin and nicotinic acetylcholine receptors [81]. In addition, several neurosteroids have affinity for the sigma-1 receptor; for example, DHEA, DHEA-S and PREG are all sigma-1 receptor agonists, while progesterone is an antagonist [21, 82, 20]. Neurosteroids therefore, appear to be highly relevant to the pathophysiology and pharmacological treatment of mood disorders, psychosis and dementia [83]. We have previously shown that DHEA-S significantly attenuates PCP-induced cognitive impairment in mice, and that these effects are antagonized by co-administration of NE-100, suggesting that DHEA-S activity is generated through sigma-1 receptors [48].

5. CLINICAL REPORTS OF SIGMA-1 RECEPTOR AGONISTS IN SCHIZOPHRENIA

A previous positron emission tomography (PET) study demonstrated that in the healthy human brain, fluvoxamine (50-200 mg) and donepezil (5 or 10 mg) bind sigma-1 receptors in a dose-dependent manner, after oral administration [84, 85]. Studies on post-mortem brains from schizophrenic patients, report a greatly reduced density of sigma receptors, compared with controls [86, 87], consistent with pre-clinical reports showing a lower level of sigma-1 receptors in PCP-treated mouse brains [73, 74].

Studies show that fluvoxamine adjunctive therapy improves negative symptoms in patients with schizophrenia [88-90] Table **2**. We recently, reported that fluvoxamine is effective in correcting cognitive impairment in patients with schizophrenia [91, 92]. There is also a case demonstrating the effectiveness of fluvoxamine in treating a patient with schizoaffective disorder for whom therapy with the SSRI, escitalopram, failed [93], suggesting a possible antipsychotic effect for fluvoxamine. Both pre-clinical and clinical evidence points to fluvoxamine being a promising therapeutic drug for cognitive and clinical symptoms in patients with schizophrenia. Recently, we performed a randomized double-blind trial of fluvoxamine adjunctive therapy in patients with schizophrenia and found that fluvoxamine was effective in restoring executive functions in patients [94].

Despite small sample sizes, clinical evidence suggests that the sigma-1 receptor agonists, donepezil [95-97], PREG [98, 99], and DHEA [100-104, 98, 105], could also be promising therapeutic agents for cognitive and clinical symptoms in patients with schizophrenia Table **2**, although these results are inconclusive [106, 107]. Further studies on sigma-1 receptor agonism using large cohorts need to be conducted.

Cognitive impairment is also a common feature in the prodromal state of psychosis [108]. Considering that sigma-1 receptors mediate neuroprotection and neuronal plasticity, it is likely that agonists such as fluvoxamine could reduce the risk of subsequent transition to schizophrenia in susceptible patients [109]. Very recently, we reported a case that fluvoxamine was effective in preventing persons at ultra-high risk of psychotic disorder from the onset of psychosis [110]. Randomized, double-blind, placebo-controlled studies of fluvoxamine in this group of patients will be necessary to determine the drug's clinical efficacy.

6. POTENTIAL THERAPEUTIC DRUGS FOR MAJOR DEPRESSIVE DISORDER

In the late 1990s, it was demonstrated that sigma-1 receptor ligands have antidepressant-like action in animal models of depression. The selective sigma-1 receptor agonist, SA4503 [53], decreases immobility time in the forced swim test without any effect on open-field locomotion [111]. Interestingly, the antidepressant-like effect of SA4503 is achieved after a single dose of the drug. A Phase II study of SA4503, in patients with major depression is currently underway. The rapid antidepressant-like action of SA4503 has more recently been replicated by different agonists such as OPC-14523, igmesine (JO1784), (+)-SKF-10,047 and DHEA-S [112, 113]. Electrophysiological studies demonstrate a rapid antidepressant-like action for sigma-1 receptor agonists [114]. In addition, sigma-1 receptor knock-out mice show longer immobility times in the forced swim test, an indicator of a depression-like phenotype in mice [115]. These results point towards rapid antidepressant-like activity for sigma-1 receptor agonists [20].

The NMDA receptor antagonist ketamine exerts a rapid antidepressant action in patients with refractory major depression and bipolar depression [116, 117]. It is possible that this activity is triggered by sigma-1 receptor agonist binding [70, 71], since ketamine has moderate affinity for this receptor [118, 119].

7. CLINICAL REPORTS OF SIGMA-1 RECEPTOR AGONISTS IN PSYCHOTIC DEPRESSION

Psychotic (or delusional) major depression is a severe illness typified by marked depressive symptoms and accompanied by delusions, and sometimes, by hallucinations. Patients with psychotic depression tend to experience longer episodes, psychomotor impairment, guilt, suicidal pre-occupation, and cognitive impairment [120-122]. In addition, they have a significantly higher mortality than patients with nonpsychotic major depression [121, 123, 124]. Several reports link psychotic depression with higher cortisol levels and more severe cognitive impairment, relative to non-psychotic depression sufferers [125-127].

Unfortunately for patients, psychotic depression frequently proves difficult to treat. Clinical studies demonstrate the efficacy of combined antidepressant (either a TCA or an SSRI) and atypical antipsychotic or electroconvulsive therapy (ECT) in treating psychotic depression [120, 124]. However, combinations of antipsychotics can lead to severe side effects such as extrapyramidal symptom or tardive dyskinesia [124]. Additionally, several antidepressants, *e.g.* TCAs, can produce significant cognitive impairment [128]. Several case reports have found that fluvoxamine monotherapy, in contrast to other SSRIs, is effective in treating patients with psychotic depression [129-131]. Furthermore, fluvoxamine monotherapy has a superior efficacy in alleviating both the psychotic and depressive symptoms of this disorder [132-136] Table **3**, while paroxetine has a lesser effect [137].

Sigma-1 receptors have been implicated in the pathophysiology of depression and in the therapeutic action of antidepressants [18, 30]. Unlike paroxetine, with an inhibition constant (Ki) of 1,893

Table 2. Clinical Studies Using Sigma-1 Receptor Agonists in Schizophrenia

Compound	Study Design	Sample Size	Dose (mg)	Positive Symptoms	Negative Symptoms	Cognitive Symptoms	Ref.
Fluvoxamine	DBT, RCT	30	100	→	↑	NA	[88]
	DBT, RCT	25	100	→	↑	NA	[89]
	DBT, RCT	53	100	→	↑	NA	[90]
	DBT, RCT	44	150	→	→	↑	[94]
Donepezil	DBT, RCT, COT	15	5	↑ (PANSS total score)		↑	[95]
	DBT, RCT, COT	13	5-10	NA	↑(depressive symptom)	NA	[96]
	DBT, RCT, COT	13	5-10	→	↑	NA	[97]
DHEA	DBT, RCT	27	100	→	↑	NA	[100]
	DBT, RCT, COT	55	200	→	→	↑	[102]
	DBT, RCT	31	150	→	↑	→	[103]
PREG	DBT, RCT	18	500	→	↑	→	[98]
PREG DHEA	DBT, RCT	44	30 200 400	↑ → →	→ → →	↑ → →	[105]

DBT: Double-blind trial, RCT: Randomized controlled trial, COT: Cross-over trial, ↑: Effective, →: No change, NA: Not assessed, PANSS: The Positive and Negative Syndrome Scale.

nM, fluvoxamine is a potent sigma-1 receptor agonist with a Ki of 36 nM [45]. Fluvoxamine, but not paroxetine, binds to sigma-1 receptors in the intact human brain [84], suggesting that sigma-1 receptors are involved in fluvoxamine's mode of action. Supporting this is the evidence that fluvoxamine, but not paroxetine, improves PCP-induced cognitive impairment in mice [48] and cognitive impairment in some schizophrenics [91, 92]. As in schizophrenia, patients with psychotic depression have a greater level of cognitive impairment compared with non-psychotic depression [125-127]. In summary, the superior efficacy of fluvoxamine monotherapy in psychotic depression may be due to its sigma-1 receptor agonist property [138, 139, 30]. Again, further studies are needed to confirm the role of sigma-1 receptors in the efficacy of fluvoxamine treatment of psychotic depression.

8. CLINICAL REPORTS OF FLUVOXAMINE IN DELIRIUM

Delirium, a common and deleterious complication in patients, is thought to be a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of the neurotransmitters that normally control cognitive function, behavior, and mood [140]. Recently, Furuse and Hashimoto [141-143] reported that fluvoxamine is effective in treating the delirium associated with Alzheimer's disease and patients in intensive care units, and postoperative delirium, although these reports are case reports. Given the role of sigma-1 receptors in the regulation of neurotransmitters as well as in cognition [27, 30, 20], it is likely that again, they are the target of fluvoxamine's therapeutic action [144]. In order to confirm the role of sigma-1 receptors in the treatment of delirium, a randomized double-blind, placebo-controlled study of selective sigma-1 receptor agonists (for example, SA4503) in patients with delirium would be of interest.

9. CONCLUSION

As discussed here, sigma-1 receptors play a role in neuroplasticity and regulation of various neurotransmitter systems, and may be implicated in the pathophysiology of cognitive impairment in neuropsychiatric diseases. This would make sigma-1 receptor agonists attractive therapeutic drugs in the improvement of cognitive impairment, especially in schizophrenia and psychotic depression. The evolution of more selective sigma-1 receptor agonists and the analysis of their efficacy in the treatment of cognitive impairment associated with neuropsychiatric diseases are still needed.

ABBREVIATIONS

AChE	=	Acetylcholinesterase
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP	=	Adenosine triphosphate
CNS	=	Central nervous system
DHEA	=	Dehydroepiandrosterone
DHEA-S	=	Dehydroepiandrosterone-sulphate

Table 3. Clinical Studies Using Fluvoxamine in Psychotic Depression

Study Design	Analyzed Sample Size	Duration of Administration	Dose (mg)	Evaluation Criteria	Efficacy (%)	Ref.
Open	59	6 weeks	300	HAM-D<=8 DDERS=0	84.2	[133]
Open	25	6/ 24 months (30 months)	300/ 200	Rate of recurrence	0/ 20	[134]
DBT, RCT	Flu+Pla: 36 Flu+Pin: 36	6 weeks	Flu: 300 Pin: 7.5	HAM-D<=8 DDERS=0	80.0 80.5	[135]
DBT, RCT	Flu: 14 Ven: 14	6 weeks	Flu: 300 Ven: 300	HAM-D<=8 DDERS=0	Flu: 78.6 Ven: 58.3	[136]
DBT, RCT	Flu+Pla: 13 Flu+Hal: 11 Des+Pla: 10 Des+Hal: 14	6 weeks	Flu: 300 Des: 150 Hal: 0.1mg/kg	HAM-D<=50% DDERS=0	Flu+Pla: 69 Flu+Hal: 45 Des+Pla: 40 Des+Hal: 64	[132]

DBT: Double-blind trial, RCT: Randomized controlled trial, HAM-D: Hamilton rating scale for depression, DDERS: Dimensions of delusional experience rating scale, Flu: Fluvoxamine, Pla: Placebo, Pin: Pindolol, Ven: Venlafaxine, Des: Desipramine, Hal: Haloperidol.

ECT = Electroconvulsive therapy
ER = Endoplasmic reticulum
$GABA_A$ = γ-aminobutyric acid type A
IP_3 = Inositol 1,4,5-triphsphate
NGF = Nerve-growth factor
NMDA = *N*-Methyl-D-aspartate
PCP = Phencyclidine
PET = Positron emission tomography
PPBP = 4-phenyl-1-(4-phenylbutyl)piperidine
(±)-PPCC = Methyl (1*R*,2*S*/1*S*,2*R*)-2-[4-hydroxy-4-phenylpiperidin-1-yl)methyl]-1-(4-methylphenyl) cyclopropanecarboxylate
PREG = pregnenolone
SA4503 = 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride
SSRI = Selective serotonin reuptake inhibitor
TCA = Tricyclic antidepressant

CONFLICT OF INTEREST

Dr. Hashimoto reports having received the speakers' bureau honoraria from Abbott Pharmaceuticals. Other authors report no competing interests.

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A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum

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ABSTRACT

While longitudinal magnetic resonance imaging (MRI) studies have demonstrated progressive gray matter reduction of the superior temporal gyrus (STG) during the early phases of schizophrenia, it remains largely unknown whether other temporal lobe structures also exhibit similar progressive changes and whether these changes, if present, are specific to schizophrenia among the spectrum disorders. In this longitudinal MRI study, the gray matter volumes of the fusiform, middle temporal, and inferior temporal gyri were measured at baseline and follow-up scans (mean inter-scan interval = 2.7 years) in 18 patients with first-episode schizophrenia, 13 patients with schizotypal disorder, and 20 healthy controls. Both schizophrenia and schizotypal patients had a smaller fusiform gyrus than controls bilaterally at both time points, whereas no group difference was found in the middle and inferior temporal gyri. In the longitudinal comparison, the schizophrenia patients showed significant fusiform gyrus reduction (left, −2.6%/year; right, −2.3%/year) compared with schizotypal patients (left: −0.4%/year; right: −0.2%/year) and controls (left: 0.1%/year; right: 0.0%/year). However, the middle and inferior temporal gyri did not exhibit significant progressive gray matter change in all diagnostic groups. In the schizophrenia patients, a higher cumulative dose of antipsychotics during follow-up was significantly correlated with less severe gray matter reduction in the left fusiform gyrus. The annual gray matter loss of the fusiform gyrus did not correlate with that of the STG previously reported in the same subjects. Our findings suggest regional specificity of the progressive gray matter reduction in the temporal lobe structures, which might be specific to overt schizophrenia within the schizophrenia spectrum.

1. Introduction

Several whole-brain magnetic resonance imaging (MRI) studies have demonstrated progressive gray matter reduction predominantly in the temporal regions in first-episode schizophrenia (Mané et al., 2009; Whitford et al., 2006), suggesting active pathological processes during the early course of the illness. More specifically, longitudinal MRI studies using manual region-of-interest (ROI) method have revealed marked gray matter loss (up to 5%/year) of the superior temporal gyrus (STG) in these patients, which is likely to underlie positive symptomatology (Kasai et al., 2003a,b; Sun et al., 2009; Takahashi et al., 2009, 2010b). On the other hand, patients with schizotypal (personality) disorder (SPD), a prototypic disorder within the schizophrenia spectrum (Siever and Davis, 2004), or affective psychosis are unlikely to exhibit progressive STG changes (Kasai et al., 2003a,b; Takahashi et al., 2010b), suggesting that such active pathological processes are specific to overt schizophrenia among the spectrum disorders. However, whether these progressive changes occur predominantly in the STG or are widely seen in the lateral temporal regions (e.g., the middle and inferior temporal gyri) has yet to be elucidated.

The fusiform gyrus, a spindle-shaped structure located on the ventral surface of the brain, is engaged in face recognition (Haxby et al., 2000, 2002; Kanwisher et al., 1997), which has been reported to be disturbed in the schizophrenia spectrum (Conklin et al., 2002; Larøi et al., 2007; Martin et al., 2005; Morris et al., 2009; Sachs et al., 2004). Previous postmortem (McDonald et al., 2000) and MRI (Lee et al., 2002; Onitsuka et al., 2003, 2005, 2006; Takahashi et al., 2006) studies

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CASH, Comprehensive Assessment of Symptoms and History; FG, fusiform gyrus; ICV, intracranial volume; ITG, inferior temporal gyrus; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; ROI, region-of-interest; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SPD, schizotypal personality disorder; STG, superior temporal gyrus.

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in schizophrenia have demonstrated reduced gray matter volume in this region and its relationship to a range of clinical symptoms such as both positive (Nestor et al., 2007) and negative (Nestor et al., 2007) symptoms, lack of insight (Ha et al., 2004), and cognitive deficits (Onitsuka et al., 2006). On the other hand, a few MRI studies of the fusiform gyrus in schizotypal subjects have yielded inconsistent results, with both normal (Dickey et al., 2003) and reduced (Takahashi et al., 2006) gray matter volume. A recent finding of an inverse correlation between the volume of the left fusiform gyrus and the duration of initial untreated period of first-episode psychoses (Bangalore et al., 2009) suggests a regional progressive process in the fusiform gyrus during the early stages of psychosis. To our knowledge, however, no ROI-based MRI studies have undertaken a detailed longitudinal examination of the fusiform gyrus in first-episode schizophrenia or schizotypal patients.

This longitudinal ROI-based MRI study aimed to investigate the gray matter changes of the fusiform gyrus, middle temporal gyrus, and inferior temporal gyrus in first-episode schizophrenia and schizotypal patients compared with healthy controls. On the basis of previous cross-sectional findings in these temporal lobe structures (Takahashi et al., 2006) as well as previous observation suggesting that active pathological processes of the temporal region might be specific to overt schizophrenia (Kasai et al., 2003a,b; Takahashi et al., 2010b), we predicted that only the schizophrenia patients would show progressive gray matter loss in the fusiform gyrus. We also explored possible relationships between the progressive brain changes and clinical variables (e.g., antipsychotic medication, treatment response) in first-episode schizophrenia.

2. Methods

2.1. Participants

Eighteen first-episode schizophrenia patients (12 males, 6 females), 13 schizotypal disorder patients (9 males, 4 females), and 20 control subjects (11 males, 9 females) were included in this study. All subjects were right-handed and physically healthy, and none had a history of serious head trauma, neurological illness, substance abuse disorder, or serious medical disease. Table 1 shows the demographic and clinical data of the subjects. MRI findings of the STG in the same group of subjects have been reported previously (Takahashi et al., 2010b). Of the 51 participants in this study, 48 subjects (17 schizophrenia, 12 schizotypal, and 19 control subjects) were also included in our previous cross-sectional study of temporal lobe structures (Takahashi et al., 2006). This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University. After a complete description of the study was provided, written informed consent was obtained from all subjects.

First-episode schizophrenia patients who fulfilled the ICD-10 research criteria (World Health Organization, 1993) were recruited from inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital. In accordance with the literature (Hirayasu et al., 2000; Kasai et al., 2003a,b; Schooler et al., 2005; Yap et al., 2001), first-episode patients were defined as patients experiencing their first episode of schizophrenia whose illness onset was within 1 year of baseline scanning ($N=14$) or those undergoing their first psychiatric hospitalization ($N=4$). The diagnosis of schizophrenia was confirmed at the follow-up scan for all cases.

Schizotypal disorder patients who met the ICD-10 research criteria (World Health Organization, 1993) were recruited from among patients who visited the clinics of the Department of Neuropsychiatry of Toyama University Hospital. This patient group had exhibited at least four of the schizotypal features (inappropriate affect, odd behavior, social withdrawal, magical thinking, suspiciousness, ruminations without inner resistance, unusual perceptual experiences, stereotyped thinking, and occasional transient quasi-psychotic episodes) over a period of at least two years, accompanied by distress or associated problems in their lives and required clinical care including low-dose antipsychotics. Their characteristics have been described previously (Kawasaki et al., 2004; Suzuki et al., 2005; Takahashi et al., 2006). All available clinical information and data obtained from a detailed review of the patients' clinical records and structured interviews for Comprehensive Assessment of Symptoms and History (CASH) including the chapter on premorbid or intermorbid personality (Andreasen et al., 1992) were stored in a database. The subjects were diagnosed by a consensus reached by at least two psychiatrists using these data. Although all of the schizotypal subjects in this study also fulfilled the DSM-IV criteria for schizotypal personality disorder

Table 1
Demographic and clinical data of healthy controls, schizotypal disorder patients, and first-episode schizophrenia patients.

	Control subjects ($N=20$)	Schizotypal patients ($N=13$)	Schizophrenia patients ($N=18$)	Group comparisons
Male/female	11/9	9/4	12/6	Chi-square = 0.87, $p=0.649$
Height at first scan (cm)	165.6 (7.2)	166.6 (9.5)	166.1 (6.7)	ANOVA: $F(2,48)=0.08$, $p=0.925$
Education (years)	15.1 (2.4)	12.6 (2.5)	13.0 (1.6)	ANOVA: $F(2,48)=6.58$, $p=0.003$
Parental education (years)	12.9 (2.8)	12.2 (1.7)	12.4 (2.1)	ANOVA: $F(2,48)=0.40$, $p=0.670$
Age at baseline scan (years)	23.2 (5.7) [18.0–38.0]	22.8 (5.0) [16.3–34.4]	23.1 (4.7) [17.9–31.9]	ANOVA: $F(2,48)=0.32$, $p=0.727$
Inter-scan interval (years)	2.6 (0.4) [2.0–3.2]	2.9 (0.8) [1.8–4.4]	2.7 (0.6) [1.3–3.9]	ANOVA: $F(2,48)=0.84$, $p=0.437$
Age of onset (years)	–	–	21.9 (4.7) [16.0–30.0]	–
Illness duration at baseline (months)	–	–	10.8 (9.7) [1–41] (median = 6.6)	–
Duration of medication at baseline (months)	–	38.7 (61.0) [1.2–204] (median = 10.8)	9.1 (10.4) [1–36] (median = 3.6)	ANOVA: $F(1,29)=4.12$, $p=0.052$
Drug dose (haloperidol equivalent[a])				
At baseline (mg/day)	–	4.6 (3.8)	15.7 (11.9)	ANOVA: $F(1,29)=10.36$, $p=0.003$
At follow-up (mg/day)	–	5.7 (5.0)	13.2 (10.4)	ANOVA: $F(1,29)=5.86$, $p=0.022$
Mean dose during follow-up (mg/day)	–	5.4 (4.2)	9.9 (6.8)	ANOVA: $F(1,29)=4.52$, $p=0.042$
Cumulative dose during follow-up (mg)	–	5970 (6307)	10213 (8974)	ANOVA: $F(1,29)=2.13$, $p=0.155$
Total SAPS score[b]				
Baseline	–	17.0 (9.7)	34.3 (25.2)	ANOVA: $F(1,25)=5.00$, $p=0.035$
Follow-up	–	12.1 (10.2)	20.8 (17.7)	ANOVA: $F(1,28)=2.49$, $p=0.126$
Total SANS score[b]				
Baseline	–	52.1 (21.6)	58.8 (24.2)	ANOVA: $F(1,25)=0.56$, $p=0.462$
Follow-up	–	41.8 (17.2)	38.9 (24.4)	ANOVA: $F(1,28)=0.13$, $p=0.718$

Data are presented as mean (SD) [range]. SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
[a] The different typical and atypical antipsychotic dosages are converted into haloperidol equivalents using the guideline by Toru (2001).
[b] Data missing for 4 patients (1 schizotypal and 3 schizophrenia patients) at the baseline and for 1 schizophrenia patient at the follow-up.

(SPD) on Axis II, two subjects had previously experienced transient quasi-psychotic episodes fulfilling a DSM Axis I diagnosis of brief psychotic disorder (American Psychiatric Association, 1994). The mental condition of each subject was regularly assessed by experienced psychiatrists to check for the emergence of full-blown psychotic symptoms, and none of the 13 patients has developed overt schizophrenia to date (mean clinical follow-up period after baseline scanning = 5.1 years, SD = 2.1).

The clinical symptoms of the schizophrenia and schizotypal patients were rated at the time of scanning (baseline and follow-up) using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). At the baseline, 12 schizophrenia and 6 schizotypal patients were treated with atypical antipsychotics, and 6 schizophrenia and 7 schizotypal patients were receiving typical ones. The patients were also receiving benzodiazepines (15 schizophrenia and 8 schizotypal patients), anticholinergics (14 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 6 schizotypal patients), and/or mood stabilizers [lithium carbonate (1 schizotypal patient), sodium valproate (1 schizophrenia patient), or carbamazepine (2 schizotypal patients)]. At the follow-up scan, 11 schizophrenia and 10 schizotypal patients were on atypical antipsychotics, and 7 schizophrenia and 3 schizotypal patients were on typical antipsychotics. Some patients were also receiving benzodiazepines (13 schizophrenia and 10 schizotypal patients), anticholinergics (15 schizophrenia and 9 schizotypal patients), antidepressants (1 schizophrenia and 4 schizotypal patients), and/or mood stabilizers [sodium valproate (1 schizophrenia and 1 schizotypal patients), carbamazepine (1 schizophrenia and 2 schizotypal patients), or a combination of lithium and carbamazepine (1 schizophrenia and 1 schizotypal patients)]. During the follow-up period between scans, 9 patients (4 schizophrenia and 5 schizotypal patients) were predominantly treated with typical antipsychotics, 18 patients (11 schizophrenia and 7 schizotypal patients) were treated mostly with atypical antipsychotics (although 2 patients received typical antipsychotics for <1 month), and 4 (3 schizophrenia and 1 schizotypal patients) received substantial amounts of both typical and atypical antipsychotics.

The control subjects consisted of 20 healthy volunteers recruited from members of the community, hospital staff, and university students. 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 (2 items) histories of illness. They did not have any personal or family history of psychiatric illness among their first-degree relatives.

2.2. Magnetic resonance imaging procedures

The subjects were scanned twice 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. The scanner was calibrated weekly with the same phantom to ensure measurement stability.

Image processing for volumetric analysis has been described in detail elsewhere (Takahashi et al., 2002). Briefly, on a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA), the image data were processed using the software package Dr View 5.3 (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, with a 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 gray matter, white matter, and cerebrospinal fluid. The intracranial volume (ICV) was measured to correct for differences in head size as described previously (Zhou et al., 2003).

2.3. Volumetric analyses of regions of interest (ROIs)

As described in detail elsewhere (Takahashi et al., 2006), the gray matter volume of the fusiform gyrus, middle temporal gyrus, and inferior temporal gyrus was measured on consecutive 1-mm coronal slices of segmented gray matter images (Fig. 1).

Briefly, the fusiform gyrus was traced from rostral to caudal, beginning with the slice containing the anterior tip of the parieto-occipital sulcus as seen on the midsagittal plane and ending caudally with the most anterior slice that contains the occipitotemporal sulcus. On each coronal slice, the medial and lateral boundaries were the collateral sulcus and the occipitotemporal sulcus, respectively (Kim et al., 2000; Lee et al., 2002). The fusiform gyrus was then subdivided into anterior and posterior portions by the last slice including the crus of the fornix.

For the middle and inferior temporal gyri, the slice showing the appearance of the temporal stem and that containing the anterior tip of the parieto-occipital sulcus were chosen as anterior and posterior boundaries, respectively. The superior temporal sulcus or the anterior occipital sulcus was used as the superior boundary, and the

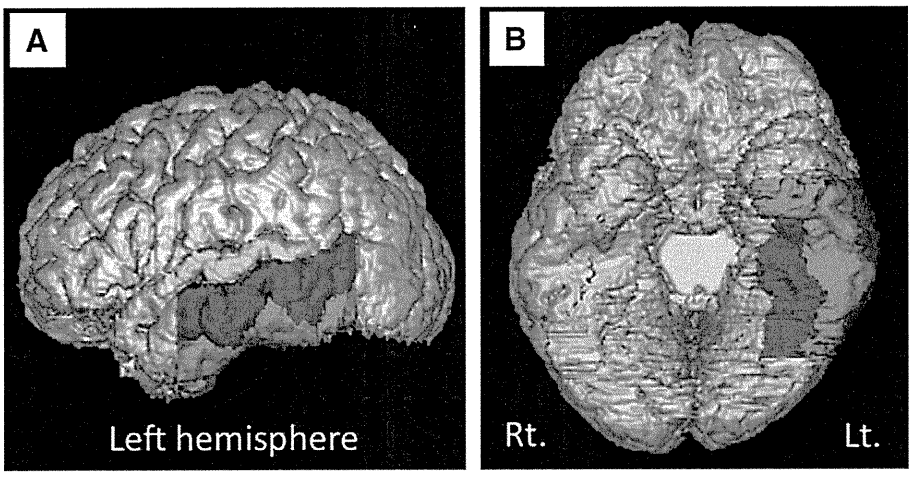

Fig. 1. Sagittal (A) and ventral (B) views of a three-dimensional reconstructed image of the temporal lobe structures. The middle (red) and inferior (green) temporal gyri and the fusiform gyrus (blue) were manually traced in this study. The superior temporal gyrus (yellow) has been measured in our previous study (Takahashi et al., 2010b) but is shown here as a reference for the topography of the temporal lobe structures.

occipitotemporal sulcus or the collateral sulcus in the area rostral to the end of the occipitotemporal sulcus was used as the inferior boundary. The middle and inferior temporal gyri were then divided into each gyrus by the inferior temporal sulcus. The course of the inferior temporal sulcus was carefully followed in three dimensions because of its frequent interruptions. In these interrupted cases, the more prominent one or the lowest one on the lateral surface if equal was used as the boundary (Kim et al., 2000).

All measurements were carried out by one rater (TT) without knowledge of the subjects' identities and the times of their scans. Inter- (TT and TR) and intra-rater intraclass correlation coefficients in a subset of 10 randomly selected brains were over 0.92.

2.4. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test. The absolute ROI volumes were analyzed using a repeated measures analysis of covariance (ANCOVA) with age, ICV, and dosage of antipsychotic medication at scanning as covariates, diagnosis as a between-subject factor, and side as a within-subject variable.

The longitudinal volume changes were analyzed using the percentage volume change [100×(absolute volume at follow-up scan − absolute volume at baseline)/absolute volume at baseline] as the dependent variable. A repeated measures ANCOVA with age at first scan, ICV, inter-scan interval, and cumulative dose of antipsychotics during scans as covariates, diagnosis as a between-subject factor, and side as a within-subject factor was performed. For the fusiform gyrus, subregion (anterior and posterior portions) was also used as a within-subject variable in these ANCOVAs. Post hoc Neumann–Keuls tests were carried out. While gender was not used as a between-subject factor owing to small sample size, especially for females, none of the ANCOVA results reported herein changed when we included gender as a covariate.

As we found significant volume changes over time only in the fusiform gyrus of first-episode schizophrenia group in this study, the correlations between the percentage volume change per year of the fusiform gyrus and the severity of clinical symptoms (absolute score change between scans and score at follow-up period of total or subscale SANS/SAPS scores) as well as cumulative dose of antipsychotics in the schizophrenia patients were analyzed using Spearman's rho. In order to examine the possible relationship of the gray matter reduction over time among temporal lobe structures in first-episode schizophrenia, Spearman's rho was calculated between the annual gray matter loss of the STG subregions (Takahashi et al., 2010b) and fusiform gyrus. For schizophrenia and schizotypal patients, the association between the relative ROI volumes (100×absolute volume/ICV) at baseline and medication effect (daily dosage, duration) was also analyzed. Statistical significance was defined as $p<0.05$.

3. Results

3.1. Demographic and clinical data

The groups were matched for age, gender, height, parental education, and inter-scan interval, but the controls had attained a higher level of education than the patients with either disorder (Table 1). While the baseline SAPS score for the schizophrenia patients was higher than that for the schizotypal patients, no significant group difference was found at follow-up, indicating relatively good response of positive symptoms to medication in our first-episode schizophrenia group (Table 1). There were significant differences in medication dosage at both time points; the schizotypal patients took significantly smaller amounts of antipsychotics than the schizophrenia patients. As ANCOVA with age as a covariate showed that the schizotypal patients had a larger ICV compared with the schizophrenia patients ($p=0.015$) and controls ($p=0.017$) [$F(2, 47)=3.65$, $p=0.034$], we controlled for ICV for all group comparisons of the ROIs examined in this study.

3.2. Cross-sectional comparison

ANCOVAs of the fusiform gyrus showed significant main effect of diagnosis at both time points [baseline, $F(2, 45)=5.75$, $p=0.006$; follow-up, $F(2, 45)=4.51$, $p=0.016$], but there were no significant interactions involving side ($p>0.369$) or subregion ($p>0.263$). Post-hoc analyses showed that both schizophrenia (baseline, $p=0.014$; follow-up, $p<0.001$) and schizotypal (baseline, $p=0.017$; follow-up, $p=0.010$) patients had significantly smaller fusiform gyrus volume than the controls, whereas no difference was found between these patient groups (baseline, $p=0.658$; follow-up, $p=0.170$).

For the middle and inferior temporal gyri, ANCOVAs revealed no main effect of diagnosis or side-by-diagnosis interaction at both baseline and second scan ($F=0.01$ to 1.03, $p=0.363$ to 0.994).

3.3. Longitudinal comparison

For the fusiform gyrus, ANCOVA showed a significant group difference [$F(2, 44)=10.03$, $p<0.001$], with the schizophrenia patients having a greater gray matter loss over time than the controls ($p<0.001$) or schizotypal patients ($p<0.001$) (Table 2, Fig. 2). However, no difference was found between the schizotypal patients and controls ($p=0.337$). There were no main effects of side [$F(1, 48)=0.39$, $p=0.533$] and subregion [$F(1, 48)=0.50$, $p=0.482$] or interactions involving these factors (all $p>0.254$), suggesting that volume changes of the fusiform gyrus were not highly localized to specific subregions. The fusiform gyrus volume changes over time did not differ between the patients who were predominantly treated with typical ($N=9$) and atypical ($N=18$) antipsychotics during the follow-up period [$F(1, 21)=0.18$, $p=0.679$].

There was no group difference for the middle [$F(2, 44)=0.05$, $p=0.949$] and inferior [$F(2, 44)=0.36$, $p=0.701$] temporal gyri.

When we used all available temporal ROI volumes (superior, middle, and inferior temporal gyri and fusiform gyrus) as the within-subject variable in a repeated measures ANCOVA model, there were significant main effects of diagnosis [$F(2, 44)=3.90$, $p=0.028$] and ROI [$F(3, 144)=2.93$, $p=0.036$] and a diagnosis-by-ROI interaction [$F(6, 144)=4.28$, $p<0.001$]. Post-hoc analyses showed that the fusiform gyrus and STG exhibited greater gray matter reduction over time compared with middle (fusiform gyrus, $p<0.001$; STG, $p=0.006$) and inferior (fusiform gyrus, $p<0.001$; STG, $p=0.006$) temporal gyri in first-episode schizophrenia. However, there was no significant difference in their progressive volume changes between the fusiform gyrus and STG ($p=0.518$) (see Table 2).

3.4. Correlational analysis

In the schizophrenia patients, annual gray matter reduction of the left posterior fusiform gyrus was correlated with higher total SANS score at follow-up (rho = 0.56, $p=0.019$), but this correlation did not survive Bonferroni correction for multiple comparisons. A higher cumulative dose of antipsychotics during follow-up was significantly correlated with less severe gray matter reduction in the left fusiform gyrus (rho = −0.55, $p=0.019$). There was no medication effect (duration and daily dosage at scanning) on the baseline volume of the temporal lobe structures in the schizophrenia patients (rho = −0.21 to 0.20, $p=0.43$ to 0.97), while medication duration at the baseline in the schizotypal group was correlated with left middle temporal gyrus volume (rho = −0.66, $p=0.014$).

We also examined the association between the annual gray matter loss of the fusiform gyrus and STG subregions for first-episode

Table 2
Absolute gray matter volume of the whole brain and temporal lobe structures at the baseline and the second scan and the annual percent change.

Brain region	Control subjects			Schizotypal patients			Schizophrenia patients		
	Baseline	Second Scan	% change/y	Baseline	Second Scan	% change/y	Baseline	Second Scan	% change/y
Whole gray matter	697,069 (69,538)	693,464 (77,687)	−0.3 (1.2)	743,076 (71,627)	723,953 (50,955)	−0.9 (2.1)	684,184 (83,120)	664,053 (67,613)	−0.9 (1.8)
Whole FG									
Left	9197 (1622)	9193 (1478)	0.1 (2.2)	8245 (1315)	8133 (1433)	−0.4 (1.8)	7685 (1605)	7184 (1495)	−2.6 (2.3)
Right	9024 (1792)	9004 (1671)	0.0 (1.2)	7819 (1391)	7786 (1408)	−0.2 (1.1)	7993 (1487)	7557 (1493)	−2.3 (2.3)
Anterior FG									
Left	5157 (991)	5155 (903)	0.1 (2.2)	5103 (1300)	5048 (1457)	−0.5 (2.3)	4649 (1295)	4297 (1133)	−2.9 (2.4)
Right	5127 (1082)	5108 (1004)	0.0 (1.5)	4655 (900)	4665 (929)	−0.1 (1.1)	4756 (1071)	4467 (1033)	−2.5 (2.7)
Posterior FG									
Left	4039 (1084)	4038 (1084)	0.0 (2.7)	3142 (736)	3084 (643)	−0.3 (2.1)	3036 (918)	2887 (868)	−2.1 (2.9)
Right	3897 (909)	3896 (874)	0.1 (1.3)	3164 (764)	3121 (763)	−0.4 (1.7)	3237 (799)	3090 (817)	−2.0 (2.7)
STG									
Left	12,443 (1800)	12,397 (1762)	0.0 (1.3)	10,808 (1406)	10,563 (1356)	−0.6 (3.6)	10,795 (1992)	10,023 (1701)	−2.8 (2.8)
Right	10,631 (1219)	10,650 (1347)	−0.1 (1.5)	9926 (1272)	9732 (898)	−0.3 (3.3)	9356 (1658)	8972 (1436)	−1.5 (2.7)
MTG									
Left	14,462 (2467)	14,483 (2713)	−0.2 (1.6)	15,517 (1892)	15,442 (1707)	0.1 (2.0)	14,794 (2929)	14,681 (2951)	−0.2 (1.6)
Right	15,323 (2180)	15,186 (2152)	−0.4 (1.2)	16,693 (2007)	16,545 (1952)	−0.2 (1.8)	15,182 (2800)	15,003 (2493)	−0.3 (1.8)
ITG									
Left	12,814 (2288)	12,749 (2611)	−0.5 (2.0)	13,596 (3046)	13,454 (3130)	−0.1 (2.0)	12,377 (2419)	12,285 (2223)	−0.3 (1.7)
Right	12,026 (1746)	11,921 (1936)	−0.4 (1.6)	12,752 (1601)	12,626 (1650)	−0.4 (1.1)	11,526 (2059)	11,366 (1744)	−0.3 (2.0)

Data are presented as mean (SD). Values indicate absolute volumes (mm3) except % change/year values. FG, fusiform gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus.
% change/year was calculated as follows: [100 × (absolute volume at follow-up − absolute volume at baseline)/absolute volume at baseline]/inter-scan interval. Negative value indicates decrease in volume. To demonstrate the regional volume changes within the temporal lobe structures, the previously published data of the STG (Takahashi et al., 2010b) are also shown here.

schizophrenia, but no significant correlation was found (rho = −0.12 to 0.42, $p = 0.08$ to 0.83).

4. Discussion

This longitudinal ROI-based MRI study examined the gray matter changes of the temporal lobe structures including the fusiform gyrus in first-episode schizophrenia and schizotypal disorder patients. Both patient groups had significantly smaller fusiform gyrus, but not middle and inferior temporal gyri, as compared with healthy controls at baseline, possibly reflecting a common neurobiological basis of schizophrenia susceptibility. In a longitudinal comparison, only schizophrenia patients showed further ongoing gray matter reduction in the fusiform gyrus, which might be related to the differences in phenomenology between schizophrenia and a milder form of the spectrum disorders. While we have previously reported marked STG gray matter reduction over time specifically in first-episode schizophrenia (Takahashi et al., 2010b), the middle and inferior temporal gyri did not exhibit progressive changes in the same group of subjects. The present findings thus support the regional specificity of the

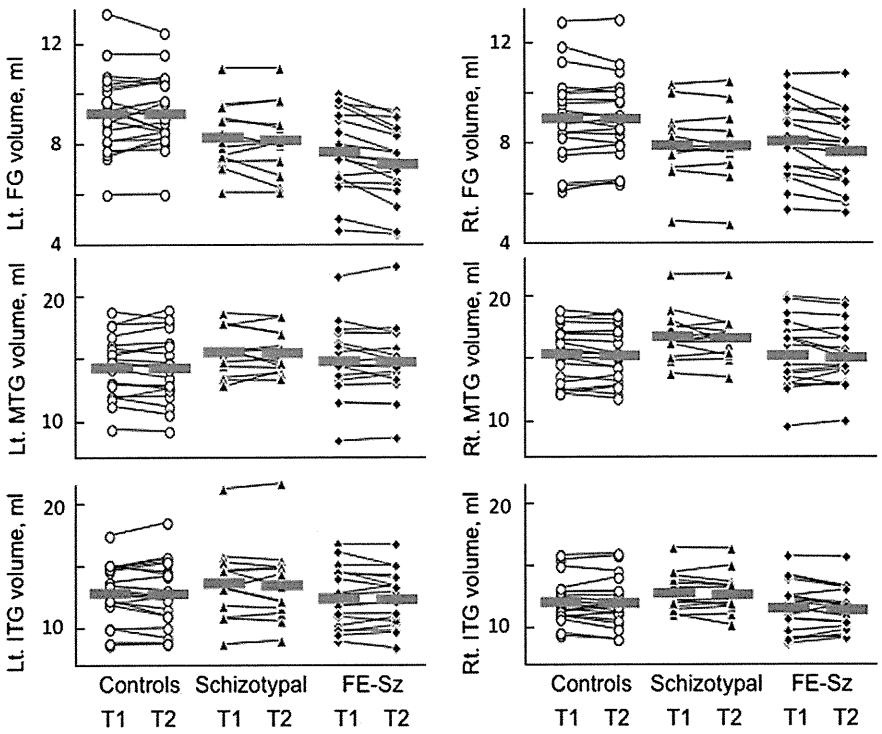

Fig. 2. Progressive volume changes of the temporal lobe structures in healthy controls, patients with schizotypal disorder, and first-episode patients with schizophrenia (FE-Sz). Values of baseline (T1) and follow-up (T2) scans in each subject are connected with a straight line. Horizontal bars indicate the means of each group. FG, fusiform gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus.