ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a disorder of the central nervous system that is estimated to occur in 3–7% of school-age children. Neurobiological studies have reported that prefrontal dysfunction is a component of the pathophysiology of ADHD.

Near-infrared spectroscopy (NIRS) is a non-invasive optical tool for studying oxygenation and hemodynamic changes in the cerebral cortex. NIRS allows researchers to measure changes in oxygenated hemoglobin, and thus, enables functional imaging of brain activity.[1] In addition to measuring changes in the concentration of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), NIRS can be used to measure changes in the redox state of cytochrome-c-oxidase, based on specific spectra in the near-infrared range (i.e., 700–1000 nm). Because of neurovascular coupling,[2,3] brain activation leads to an increase in cerebral blood flow without a proportionate increase in oxygen consumption. Consequently, an increase in the concentration of oxy-Hb is associated with a decrease in the concentration of deoxy-Hb.[1] NIRS is a neuroimaging modality that, according to Matsuo *et al.*,[4] is especially suitable for psychiatric patients for the following reasons. First, NIRS is relatively insensitive to motion artifact, and so it can be used in experiments where motion is expected, such as those involving vocalizations. Second, NIRS can be used to measure participants who are seated in a natural position, with minimal environmental distractions. Third, NIRS has a cheaper running cost than other neuroimaging modalities and is simple to set up and use. Fourth, the high temporal resolution of NIRS is useful for characterizing the time course of prefrontal activity in people with psychiatric disorders.[5,6] Accordingly, NIRS has been used to assess brain function in people with many psychiatric disorders, including schizophrenia, bipolar disorder, depression, obsessive–compulsive disorder, dementia, post-traumatic stress disorder, pervasive developmental disorder, and ADHD.[4–14]

In pediatric ADHD, reduced prefrontal hemodynamic response has been reported as measured by NIRS.[15,16] Negoro *et al.*[17] used NIRS to examine prefrontal hemodynamic activity during the Stroop Color–Word Task in 20 children with ADHD and 20 healthy age- and sex-matched controls. They found that the oxy-Hb changes in the inferior prefrontal cortex in the control group were significantly larger than those in the ADHD group during the Stroop Color–Word Task.

Atomoxetine (ATX), approved in Japan for the treatment of pediatric ADHD in April 2009, is a nonstimulant that is thought to act presynaptically via the inhibition of norepinephrine reuptake. ATX has a limited effect on serotonin and dopamine transporters and has low affinity for dopaminergic, muscarinic-cholinergic, histaminic, serotonergic, and α1- or α2-adrenergic receptors. Multiple reports have indicated that this medication is a safe and well-tolerated intervention for pediatric ADHD.[18,19] In a recent functional magnetic resonance imaging (fMRI) study, ATX was associated with increased activation in the dorsolateral prefrontal cortex, parietal cortex, caudate, and cerebellum of adults with ADHD.[20] In an NIRS study, Araki *et al.*[21] examined the effects of long-term treatment with ATX on prefrontal hemodynamic activity in 12 children with ADHD during a continuous performance task. They found that the oxy-Hb concentration in the right dorsolateral prefrontal cortex in the post-ATX condition was significantly increased compared to the pre-ATX condition.

The Stroop Color–Word Task is one of the most commonly used tools for determining attentional problems. It is also a test of executive function and working memory. The continuous performance task that was used in the previous NIRS study by Araki *et al.*[21] also measures a person's attention. However, the neuropsychological background is different. The continuous performance task mainly measures a person's sustained attention, which is associated with impulsivity. The Stroop Color–Word Task mainly measures a person's selective attention and an effect of interference. Furthermore, in another recent study, there was a different effect on the blood oxygenation level–dependent activity in the prefrontal cortex in a comparison between the Stroop Color–Word Task and the continuous performance task.[22] Thus, it is important to examine the effects of ATX on prefrontal hemodynamic activity in children with ADHD using NIRS during the Stroop Color–Word Task. In addition to these reasons, we used the Stroop Color–Word Task for the following reasons. First, the inferior frontal gyrus has been described as one of the regions most strongly related to Stroop interference.[23] Second, in the NIRS study using the same task, Negoro *et al.*[17] concluded that the word-reading task and the incongruent color-naming task produced suitable prefrontal brain activation in healthy children.

To the best of our knowledge, there are no existing reports on ATX-induced changes in prefrontal hemo-

dynamic activity in pediatric ADHD, as measured by NIRS using the Stroop Color–Word Task. Thus, we used NIRS to examine the effects of a clinical dose of ATX on changes in prefrontal hemodynamic activity during the Stroop Color–Word Task in children with ADHD.

METHODS

Participants

Ten participants (seven boys and three girls), aged 7–13 years and diagnosed with ADHD according to the DSM-IV-TR,[24] participated in the present study. The participants with ADHD, who had no history of treatment for a developmental disorder, had consulted an experienced pediatric psychiatrist at the Department of Psychiatry at Nara Medical University with the chief complaint of inattention, hyperactivity, or impulsiveness. These participants underwent a standard clinical assessment comprising of a psychiatric evaluation, a semi-structured diagnostic interview (the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version),[25] and a medical history assessment. Two experienced pediatric psychiatrists confirmed the diagnosis of ADHD according to the DSM-IV-TR. Intellectual level was assessed using the Wechsler Intelligence Scale for Children–Third Edition, and individuals with full-scale IQ (FIQ) scores below 70 were excluded. We also excluded those who presented with a comorbid Axis I diagnosis, a neurological disorder, a head injury, a serious medical condition, or a history of substance abuse/dependence. Consequentially, two individuals with chronic tic disorder were excluded. In total, 10 participants with ADHD who had no previous medication history were enrolled in the present study. All participants were right-handed and of Japanese descent.

We used NIRS to measure the relative concentrations of oxy-Hb in the participants in the drug-naïve condition (pre-treatment) and after 8 weeks of treatment with ATX (post-treatment). All measurements were conducted at the same time of day (10.00–11.00 hours). We estimated the severity of ADHD symptoms on the same day as NIRS measurement. The participants were treated with ATX as quickly as possible after completing the baseline NIRS measurement. The daily dose of ATX ranged from 10 to 75 mg (mean ± SD, 1.34 ± 0.75 mg/kg). The characteristics of the participants are shown in Table 1. This study was approved by the Institutional Review Board at Nara Medical University (approval number 354). Written informed consent was obtained from all participants and/or their parents prior to the study.

Assessment of ADHD symptoms

We used the ADHD Rating Scale-IV-Japanese version (ADHD RS-IV-J) (Home Version)[26] to evaluate ADHD symptoms in the participants. A higher

Table 1. Participant characteristics

	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	*P*-value
Number [sex ratio: M : F]	10 [7:3]		
Age (years)	9.90 (2.38)		
FIQ (WISC-III)	94.70 (10.30)		
Atomoxetine dose (mg/kg)		1.34 (0.75)	
ADHD RS-IV-J total score	30.70 (10.81)	22.60 (12.27)	0.003
SCWC-1	29.00 (12.82)	37.10 (17.28)	0.005
SCWC-2	31.80 (14.32)	36.00 (15.28)	0.004
SCWC-3	28.60 (12.95)	36.60 (14.01)	0.002

Two-tailed paired *t*-test.
ADHD RS-IV-J, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version; F, female; FIQ (WISC-III), full-scale IQ score on the Wechsler Intelligence Scale for Children–Third Edition; M, male; SCWC-1, Stroop Color–Word Task number of correct answers first time; SCWC-2, Stroop Color–Word Task number of correct answers second time; SCWC-3, Stroop Color–Word Task number of correct answers third time.

ADHD RS-IV-J score is associated with more severe ADHD symptoms. All participants underwent ADHD RS-IV-J assessment pre- and post-treatment (Table 1).

Stroop Color–Word Task

The traditional Stroop Task was combined with the word-reading task, incongruent color-naming task, and the color-naming task. However, we reconstructed the Stroop Task according to previously described methods.[27] The Stroop Color–Word Task consisted of two pages stapled together: each page had 100 items in five columns of 20 items each and the page size was 210 × 297 mm. On the first page, the words RED, GREEN, and BLUE were printed in black ink. On the second page, the words RED, GREEN, and BLUE were printed in red, green, or blue ink, with the limitation that the word meaning and ink color could not match. The items on both pages were randomly distributed, with the exception that no item could appear directly after the same item within a column.

Before the task, the examiners instructed the participants as follows: 'This is to test how quickly you can read the words on the first page, and say the colors of the words on the second page. After we say "begin," please read the words in the columns, starting at the top left, and say the words/colors as quickly as you can. After you finish reading the words in the first column, go on to the next column, and so on. After you have read the words on the first page for 45 s, we will turn the page. Please repeat this procedure for the second page.'

The entire Stroop Color–Word Task sequence consisted of three cycles of 45 s spent reading the first page and 45 s spent reading the second page (the color–word task). The task ended with 45 s spent reading the first page, which we designated as the baseline task. We recorded the number of correct answers in each cycle, and refer to them as follows: Stroop Color–Word Task number of Correct answers first time (SCWC-1), second time (SCWC-2), and third time (SCWC-3). Examiners who were blind to the diagnoses of the participants administered the Stroop Color–Word Task.

The Stroop Task used in this study was different from the traditional Stroop Task. We made the Stroop Color–Word Task simple because the participants were school-aged children. Furthermore, we excluded the color-naming task (part of the traditional Stroop Task) because we wanted to have only two tasks (baseline task and activation task) for our NIRS study.

NIRS measurements

Increased oxy-Hb and decreased deoxy-Hb, as measured by NIRS, have been shown to reflect cortical activation. In animal studies, oxy-Hb is the most sensitive indicator of regional cerebral blood flow because the direction of change in deoxy-Hb is determined by the degree of changes in venous blood oxygenation and volume.[28] Therefore, we decided to focus on changes in oxy-Hb. We measured oxy-Hb using a 24-channel NIRS machine (Hitachi ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). We measured the absorption of two wavelengths of near-infrared light (760 and 840 nm). Oxy-Hb was calculated as previously described.[29] The inter-probe intervals of the machine were 3.0 cm, and previous reports have established that the machine measures at a point 2–3 cm beneath the scalp, that is, the surface of the cerebral cortex.[10,30]

The participants were asked to adopt a natural sitting position for NIRS measurement. The distance between the eye of the participant and the paper on which items were listed was coordinated from 30 cm to 40 cm. The NIRS probes were placed on the scalp over the prefrontal brain regions, and arranged to measure the relative changes in Hb concentration at 24 measurement points that made up an 8 × 8-cm square. The lowest probes were positioned along the Fp1–Fp2 line according to the international 10/20 system commonly used in electroencephalography. The correspondence between the probe positions and the measurement points in the cerebral cortex were confirmed by superimposing the probe positions onto a three-dimensionally reconstructed cerebral cortex of a representative participant in the control group, obtained via MRI (Fig. 1). The absorption of near-infrared light was measured with a time resolution of 0.1 s. The data were analyzed using the 'integral mode': the pre-task baseline was determined as the mean across the 10 s just before the task period, the post-task baseline was determined as the mean across the 25 s immediately after the task period, and linear fitting was performed on the data between the two baselines. Moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average window, 5 s).

We attempted to exclude motion artifacts by closely monitoring artifact-evoking body move-

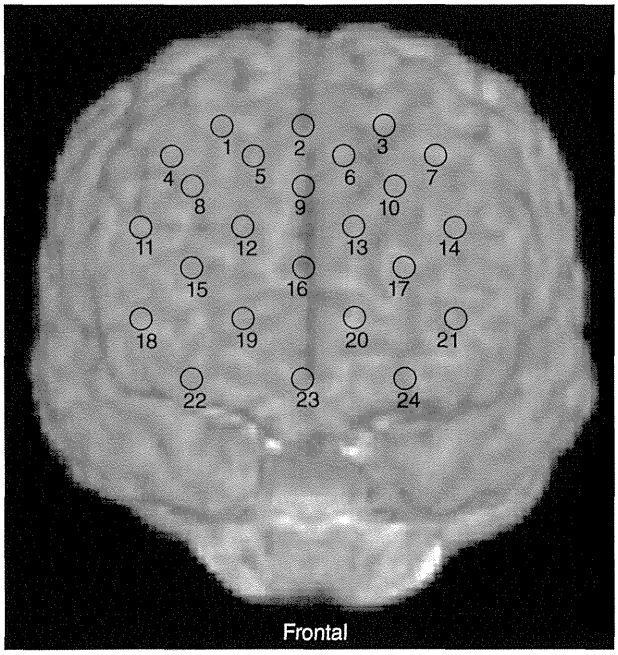

Figure 1. Near-infrared spectroscopy measurement points. The points were mapped onto the frontal lobes using MRIcro software (MRIcro was developed by Dr Chris Rorden, and is available at http://www.mricro.com). The numbers denote the channel for each measurement point.

ments, such as neck movements, biting, and blinking (identified as being the most influential in a preliminary artifact-evoking study), and by instructing the participants to avoid these movements during the NIRS measurements. Examiners were blind to the treatment condition of the participants.

Statistical analyses

For statistical comparison of the participant characteristics between the pre- and post-treatment conditions, we used a two-tailed paired *t*-test. Specifically, we compared oxy-Hb changes between the pre- and post-treatment conditions. We used PASW Statistics 18.0 J for Windows (SPSS, Tokyo, Japan) for statistical analysis. To conduct a more detailed comparison of oxy-Hb changes along the time course of the task, we used MATLAB 6.5.2 (Mathworks, Natick, MA, USA) and Topo Signal Processing type-G version 2.05 (Hitachi Medical Corporation, Tokyo, Japan). As we performed 24 paired *t*-tests, the correction for multiple comparisons was made using the false discovery rate (FDR)[31] (two-tailed; we set the value of q specifying the maximum FDR to 0.15, so that there were no more than 15% false positives on average).

RESULTS

As shown in Table 1, the SCWC-1, SCWC-2, and SCWC-3 scores in the post-treatment condition were significantly higher to those in the pre-treatment condition ($t = -3.72$, d.f. = 9, $P = 0.005$; $t = -3.81$, d.f. = 9, $P = 0.004$; $t = -4.28$, d.f. = 9, $P = 0.002$). Additionally, the total ADHD RS-IV-J scores in the post-treatment condition were significantly lower than scores in the pre-treatment condition ($t = 4.03$, d.f. = 9, $P = 0.003$).

Figure 2 shows the grand average waveforms of oxy-Hb concentration changes during the Stroop Color–Word Task in the pre- and post-treatment conditions. We found that the amplitude of the grand average waveforms of oxy-Hb concentration changes increased during the task period in the post-treatment condition, although this was not the case in the pre-treatment condition. As shown in Table 2, we found that the difference in mean oxy-Hb measurements between the task and post-task periods was significantly larger in the post-treatment than in the pre-treatment conditions at channels 11 and 21 (FDR-corrected P: 0.0063–0.0125). Figure 3 contains a topographic representation of the t-values representing the difference in oxy-Hb concentration between the pre- and post-treatment conditions during the Stroop Color–Word Task. The oxy-Hb changes in the prefrontal cortex were significantly larger in the post-treatment condition than in the pre-treatment during the task period.

We examined the correlations between the ADHD RS-IV-J scores and the difference in oxy-Hb concentration at channels 11 and 21. The decreased ADHD RS-IV-J score tended to be negatively correlated with increased oxy-Hb at channel 11 (Spearman's $\rho = -0.626$, $P = 0.097$). There was no significant correlation between the ADHD RS-IV-J score and the increased oxy-Hb at channel 21 (Spearman's $\rho = 0.427$, $P = 0.252$).

DISCUSSION

To the best of our knowledge, there are no other studies using the Stroop Task to examine ATX-induced prefrontal hemodynamic responses in pediatric ADHD as measured by NIRS. We found that oxy-Hb changes in the prefrontal cortex during the Stroop

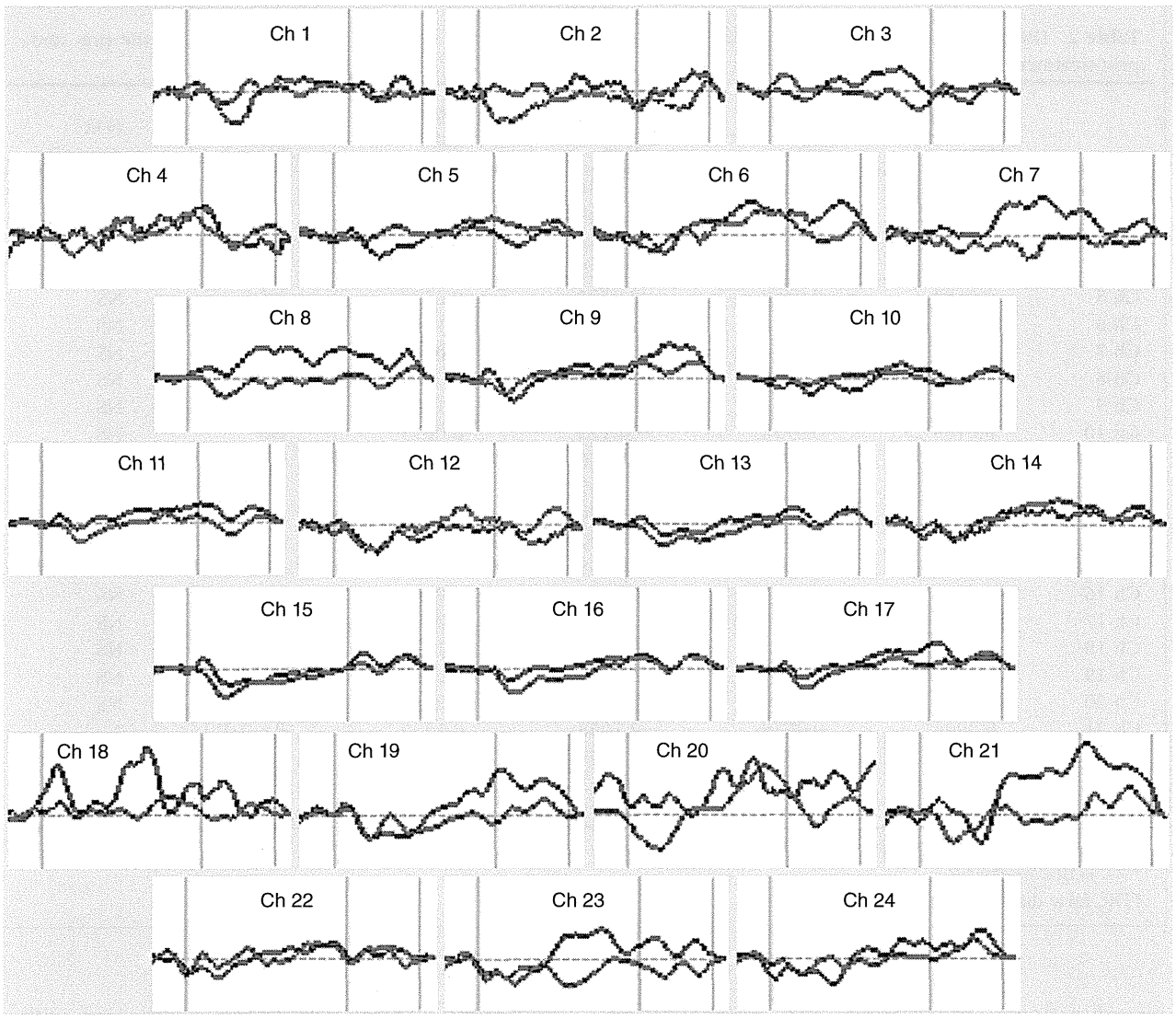

Figure 2. Grand average waveforms of oxyhemoglobin (oxy-Hb) concentration changes during the Stroop Color–Word Task in the pre- and post-treatment conditions. Red lines indicate pre-treatment and blue lines indicate post-treatment. The green lines indicate the beginning and end of each trial.

Color–Word Task were significantly larger in the post-treatment than in the pre-treatment condition. Our findings are consistent with previous NIRS studies. Araki *et al.*[21] examined the effects of long-term (6 months–1 year) treatment with ATX on prefrontal hemodynamic activity in 12 children with ADHD during a continuous performance task. In the ADHD group in the post-ATX condition, significant activation was observed in the right dorsolateral prefrontal cortex and the decrease in oxy-Hb concentration in the left ventrolateral prefrontal cortex disappeared. They concluded that long-term treatment with ATX improved prefrontal hemodynamic activity in ADHD children, and NIRS may be useful for assessment of the prefrontal hemodynamic response to ATX treatment. Furthermore, our findings are consistent with previous fMRI studies. For instance, Bush *et al.*[20] reported that adults with ADHD who had received 6 weeks of ATX treatment exhibited increased activation of the dorsolateral prefrontal cortex, parietal cortex, caudate, and cerebellum during the Multi-Source Interference Task. Similarly, Cubillo *et al.*[32] examined the

Table 2. Difference in mean oxyhemoglobin measurements between the task and post-task periods in the pre- and post-treatment conditions

	Pre-treatment (mMmm)		Post-treatment (mMmm)		Student's *t*-test	FDR correction
	Mean	SD	Mean	SD		
Ch 1	0.0004	0.0587	−0.0034	0.0915	NS	NS
Ch 2	−0.0445	0.0889	0.0085	0.1205	NS	NS
Ch 3	−0.0006	0.0535	0.0144	0.1123	NS	NS
Ch 4	0.0004	0.0702	0.0129	0.0654	NS	NS
Ch 5	0.0182	0.0487	−0.0123	0.0687	NS	NS
Ch 6	0.0182	0.0464	0.0434	0.1246	NS	NS
Ch 7	−0.0288	0.0814	0.0516	0.0808	NS	NS
Ch 8	−0.0118	0.0731	0.0690	0.0838	$P = 0.030$	NS
Ch 9	0.0175	0.0743	0.0100	0.1197	NS	NS
Ch 10	0.0109	0.0754	−0.0123	0.0615	NS	NS
Ch 11	−0.0076	0.0858	0.0310	0.0692	$P = 0.011$	*
Ch 12	−0.0051	0.0673	−0.0369	0.0627	NS	NS
Ch 13	−0.0176	0.0716	0.0090	0.0539	NS	NS
Ch 14	0.0341	0.0518	0.0132	0.0730	NS	NS
Ch 15	−0.0224	0.1002	−0.0069	0.0851	NS	NS
Ch 16	−0.0097	0.1155	0.0118	0.0607	NS	NS
Ch 17	0.0063	0.0569	0.0302	0.0451	NS	NS
Ch 18	0.0177	0.0510	0.0835	0.1123	NS	NS
Ch 19	−0.0128	0.0926	0.0361	0.0937	$P = 0.039$	NS
Ch 20	0.0231	0.0994	0.0882	0.2221	NS	NS
Ch 21	0.0004	0.0638	0.1058	0.1254	$P = 0.011$	*
Ch 22	0.0073	0.0697	0.0061	0.0739	NS	NS
Ch 23	−0.0467	0.0460	0.0253	0.1111	NS	NS
Ch 24	−0.0017	0.0943	0.0093	0.0803	NS	NS

Group differences tested with *t*-test and FDR correction.
*$P <$ FDR-corrected P.
FDR, false discovery rate; NS, not significant.

neurofunctional modulation and normalization effects of acute doses of ATX and methylphenidate within medication-naïve ADHD boys during working memory. They found that ATX significantly enhanced activation in the right dorsolateral prefrontal cortex relative to methylphenidate within patients, and significantly normalized underactivation of the right dorsolateral prefrontal relative to controls.

Although several imaging studies have investigated the effects of ATX, these have used a single dose in healthy humans or focused on patients with schizophrenia. In a previous fMRI study, 8 weeks of treatment with ATX produced a significant increase in working memory–related activation of the left dorsolateral prefrontal cortex in people with schizophrenia.[33] Graf *et al.*[34] examined the influence of ATX (80 mg) on the neural correlates of error processing in healthy control participants. Compared with a placebo, they found an increase in error signaling (false minus correct incongruent NoGo responses) in the bilateral inferior frontal cortex. Chamberlain *et al.*[35] used a stop-signal fMRI paradigm to measure the effects of ATX (40 mg) in 19 healthy volunteers in a double-blind placebo-controlled design. They found that ATX increased activation in the right inferior frontal gyrus when volunteers attempted to inhibit their responses. Accordingly, they concluded that ATX produces increased inhibitory control via modulation of right inferior frontal function, and thus it has implications for understanding and treating inhibitory dysfunction in people with ADHD and other disorders. Thus, it appears that ATX increases activation in the prefrontal cortex. Negoro *et al.*[17] used NIRS to examine reduced prefrontal hemody-

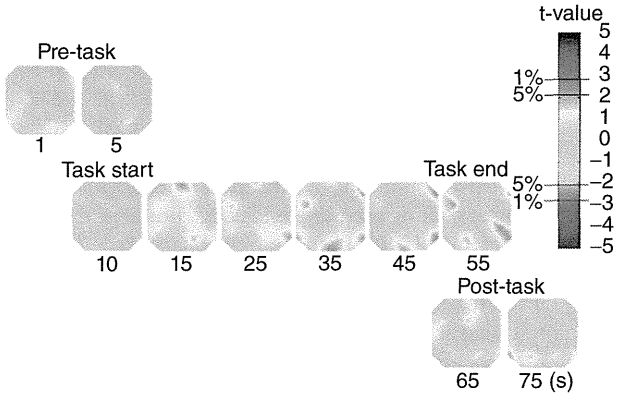

Figure 3. Topographic presentation of the t-value of the oxy-hemoglobin (oxy-Hb) comparison between the pre- and post-treatment conditions during the Stroop Color–Word Task. The t-values of oxy-Hb for the pre- and post-treatment conditions are presented as a topographic map along the time course of the task (from top to bottom). The red, green, and blue areas in the topographs indicate positive, zero, and negative t-values, with ±2.8 and ±2.1 for 1% and 5% statistical significance levels, respectively.

namic responses in ADHD children during the Stroop Color–Word Task, which is the same task used in the present study. They found that oxy-Hb changes in the inferior prefrontal cortex in individuals with pediatric ADHD were significantly lower than those in a control group. Considering the above findings, we suggest that our findings regarding larger oxy-Hb changes in the post-treatment condition indicate that ATX induced an intensified prefrontal hemodynamic response.

In the present study, at channels 11 and 21, the mean oxy-Hb difference of the post-treatment condition was significantly larger than that of the pre-treatment condition. Negoro *et al.*[17] reported a lower increase of the oxy-Hb changes at channels 8, 18, 19, 21, and 22 in individuals with pediatric ADHD compared with controls. Considering this report by Negoro *et al.*,[17] it was expected that improvement of ADHD symptoms with ATX treatment would result in increased change in the oxy-Hb in those regions; and the present finding was in line with that expectation.

In addition to the larger oxy-Hb changes, we found that total ADHD RS-IV-J scores and performance on the Stroop Color–Word Task significantly improved in the post-treatment condition. In a previous study of children with ADHD, post-treatment versus pre-treatment improvements in Stroop Test performance were statistically significant in an ATX group.[36] In a study of adults with ADHD, ATX treatment was associated with improved Stroop Color–Word score.[37] This means that ATX treatment was also associated with improved clinical symptoms in the present ADHD group. If a correlation of clinical symptom and oxy-Hb concentration changes is revealed, it will be possible to evaluate the clinical symptom and the symptomatic improvement with NIRS, which is an objective and biological tool. It is hoped that more research with a larger sample size will be conducted because there was no significant correlation between the clinical symptomatic improvement and the increased oxy-Hb in the present study.

There are three main limitations to our study. First, the spatial resolution for detecting hemodynamic responses from the scalp surface using NIRS is lower than that for fMRI, single-photon emission computed tomography, and positron emission tomography. Although the mean oxy-Hb difference of the post-treatment condition was significantly larger than that of the pre-treatment condition at channels 11 and 21, the present findings indicate that ATX treatment increased hemodynamic response in the broader prefrontal cortex, including the dorsolateral prefrontal, orbitofrontal, and frontopolar cortex, in children with ADHD. However, it is certainly significant that increased prefrontal hemodynamic response in pediatric ADHD after ATX treatment can be shown by NIRS. Second, our sample size was small. As a tentative analysis, the decreased ADHD RS-IV-J score tended to be negatively correlated with increased oxy-Hb at channel 11. However, further investigations with a larger sample size will be helpful. Third, we had no placebo-control participants. Future NIRS studies with large samples and placebo-control participants are required to determine the detailed effects of ATX, especially with respect to an intensified prefrontal hemodynamic response.

In conclusion, to the best of our knowledge, this is the first NIRS study using the Stroop Task to examine ATX-induced prefrontal hemodynamic response in individuals with pediatric ADHD. The results of the present study suggest that multi-channel NIRS systems may have potential in the pharmacotherapeutic evaluation of ATX in children with ADHD.

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REFERENCES

1. Villringer A, Chance B. Non-invasive optical spectroscopy and imaging of human brain function. *Trends Neurosci.* 1997; **20**: 435–442.
2. Villringer A, Dirnagl U. Coupling of brain activity and cerebral blood flow: Basis of functional neuroimaging. *Cerebrovasc. Brain Metab. Rev.* 1995; **7**: 240–276.
3. Gratton G, Goodman-Wood MR, Fabiani M. Comparison of neuronal and hemodynamic measures of the brain response to visual stimulation: An optical imaging study. *Hum. Brain Mapp.* 2001; **13**: 13–25.
4. Matsuo K, Kato T, Taneichi K *et al.* Activation of the prefrontal cortex to trauma-related stimuli measured by near-infrared spectroscopy in posttraumatic stress disorder due to terrorism. *Psychophysiology* 2003; **40**: 492–500.
5. Suto T, Fukuda M, Ito M, Uehara T, Mikuni M. Multichannel near-infrared spectroscopy in depression and schizophrenia: Cognitive brain activation study. *Biol. Psychiatry* 2004; **55**: 501–511.
6. Kameyama M, Fukuda M, Yamagishi Y *et al.* Frontal lobe function in bipolar disorder: A multichannel near-infrared spectroscopy study. *Neuroimage* 2006; **29**: 172–184.
7. Kubota Y, Toichi M, Shimizu M *et al.* Prefrontal activation during verbal fluency tests in schizophrenia–a near-infrared spectroscopy (NIRS) study. *Schizophr. Res.* 2005; **77**: 65–73.
8. Shinba T, Nagano M, Kariya N *et al.* Near-infrared spectroscopy analysis of frontal lobe dysfunction in schizophrenia. *Biol. Psychiatry* 2004; **55**: 154–164.
9. Fallgatter AJ, Roesler M, Sitzmann L, Heidrich A, Mueller TJ, Strik WK. Loss of functional hemispheric asymmetry in Alzheimer's dementia assessed with near-infrared spectroscopy. *Brain Res. Cogn. Brain Res.* 1997; **6**: 67–72.
10. Hock C, Villringer K, Müller-Spahn F *et al.* Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS)–correlation with simultaneous rCBF-PET measurements. *Brain Res.* 1997; **755**: 293–303.
11. Kuwabara H, Kasai K, Takizawa R *et al.* Decreased prefrontal activation during letter fluency task in adults with pervasive developmental disorders: A near-infrared spectroscopy study. *Behav. Brain Res.* 2006; **172**: 272–277.
12. Ehlis AC, Bähne CG, Jacob CP, Herrmann MJ, Fallgatter AJ. Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: A functional near-infrared spectroscopy (fNIRS) study. *J. Psychiatr. Res.* 2008; **42**: 1060–1067.
13. Okada K, Ota T, Iida J, Kishimoto N, Kishimoto T. Lower prefrontal activity in adults with obsessive-compulsive disorder as measured by near-infrared spectroscopy. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2013; **43**: 7–13.
14. Ota T, Iida J, Sawada M *et al.* Reduced prefrontal hemodynamic response in pediatric obsessive-compulsive disorder as measured by near-infrared spectroscopy. *Child Psychiatry Hum. Dev.* 2013; **44**: 265–277.
15. Weber P, Lütschg J, Fahnenstich H. Cerebral hemodynamic changes in response to an executive function task in children with attention-deficit hyperactivity disorder measured by near-infrared spectroscopy. *J. Dev. Behav. Pediatr.* 2005; **26**: 105–111.
16. Inoue Y, Sakihara K, Gunji A *et al.* Reduced prefrontal hemodynamic response in children with ADHD during the Go/NoGo task: A NIRS study. *Neuroreport* 2012; **23**: 55–60.
17. Negoro H, Sawada M, Iida J, Ota T, Tanaka S, Kishimoto T. Prefrontal dysfunction in attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Child Psychiatry Hum. Dev.* 2010; **41**: 193–203.
18. Michelson D, Faries D, Wernicke J *et al.* Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: A randomized, placebo-controlled, dose-response study. *Pediatrics* 2001; **108**: e83.
19. Spencer T, Heiligenstein JH, Biederman J *et al.* Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *J. Clin. Psychiatry* 2002; **63**: 1140–1147.
20. Bush G, Holmes J, Shin LM *et al.* Atomoxetine increases fronto-parietal functional MRI activation in attention-deficit/hyperactivity disorder: A pilot study. *Psychiatry Res.* 2013; **211**: 88–91.
21. Araki A, Ikegami M, Okayama A *et al.* Improved prefrontal activity in AD/HD children treated with atomoxetine: A NIRS study. *Brain Dev.* 2014. doi:10.1016/j.braindev.2014.03.011
22. Lesh TA, Westphal AJ, Niendam TA *et al.* Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia. *Neuroimage Clin.* 2013; **2**: 590–599.
23. Laird AR, McMillan KM, Lancaster JL *et al.* A comparison of label-based review and ALE meta-analysis in the Stroop task. *Hum. Brain Mapp.* 2005; **25**: 6–21.

24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Ed, Text Revision (DSM-IV-TR)*. American Psychiatric Association, Washington, DC, 2000.
25. Kaufman J, Birmaher B, Brent D *et al.* Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry* 1997; **36**: 980–988.
26. Yamazaki K. ADHD-RS-IV Japanese version. **In**: Kanbayashi Y, Saito K, Kita M (eds). *Japanese Guideline for the Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD)*. Jiho, Tokyo, 2003; 48–54 (in Japanese).
27. Golden CJ. A group version of the Stroop Color and Word Test. *J. Pers. Assess.* 1975; **39**: 386–388.
28. Hoshi Y, Kobayashi N, Tamura M. Interpretation of near-infrared spectroscopy signals: A study with a newly developed perfused rat brain model. *J. Appl. Physiol.* 2001; **90**: 1657–1662.
29. Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD. Alterations in the functional anatomy of working memory in adult attention-deficit/hyperactivity disorder. *Am. J. Psychiatry* 2000; **157**: 278–280.
30. Toronov V, Webb A, Choi JH *et al.* Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. *Med. Phys.* 2001; **28**: 521–527.
31. Singh AK, Dan I. Exploring the false discovery rate in multichannel NIRS. *Neuroimage* 2006; **33**: 542–549.
32. Cubillo A, Smith AB, Barrett N *et al.* Drug-specific laterality effects on frontal lobe activation of atomoxetine and methylphenidate in attention deficit hyperactivity disorder boys during working memory. *Psychol. Med.* 2014; **44**: 633–646.
33. Friedman JI, Carpenter D, Lu J *et al.* A pilot study of adjunctive atomoxetine treatment to second-generation antipsychotics for cognitive impairment in schizophrenia. *J. Clin. Psychopharmacol.* 2008; **28**: 59–63.
34. Graf H, Abler B, Freudenmann R *et al.* Neural correlates of error monitoring modulated by atomoxetine in healthy volunteers. *Biol. Psychiatry* 2011; **69**: 890–897.
35. Chamberlain SR, Hampshire A, Müller U *et al.* Atomoxetine modulates right inferior frontal activation during inhibitory control: A pharmacological functional magnetic resonance imaging study. *Biol. Psychiatry* 2009; **65**: 550–555.
36. Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and methylphenidate treatment in children with ADHD: The efficacy, tolerability and effects on executive functions. *Child Psychiatry Hum. Dev.* 2011; **42**: 257–269.
37. Faraone SV, Biederman J, Spencer T *et al.* Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 2005; **15**: 664–670.

RESEARCH ARTICLE

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Low amyloid-β deposition correlates with high education in cognitively normal older adults: a pilot study

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Objective: Several epidemiological studies have found a lower incidence of Alzheimer's disease in highly educated populations, but the protective mechanism of education against the disease is still unclear. Our objective was to investigate the association between education and ^{11}C-labeled Pittsburgh Compound B (PIB) uptake with positron emission tomography in participants with normal cognitive ability.

Methods: We performed ^{11}C-labeled PIB positron emission tomography and neuropsychological testing in 30 cognitively normal older participants. Of the participants, 16 had a period of education less than 12 years (low-education group) and 14 had more than 13 years (high-education group). Amyloid-β deposition was quantified by binding potential (BP_{ND}) in several brain regions and was compared between the groups with different education levels.

Results: We found significantly higher cortical PIB-BP_{ND} in the cognitively normal participants with low education compared with the ones with high education. None of the brain regions in low-education group showed significantly lower BP_{ND} values. This finding was not affected by the inclusion of possible confounding variables such as age, sex, and general intelligence. Our findings indicated a reduced amyloid pathology in highly educated, cognitively normal, participants.

Conclusions: Our findings lead to the proposal that early-life education has a negative association with Alzheimer's disease pathology. This proposal is not in opposition to the brain reserve hypothesis. People with more education might be prone to a greater inhibitory effect against amyloid-β deposition before the preclinical stage. At the same time, they have a greater reserve capacity, and greater pathological changes are required for dementia to manifest. Copyright © 2014 John Wiley & Sons, Ltd.

Key words: Alzheimer's disease (AD); amyloid-β (Aβ); positron emission tomography (PET); ^{11}C-labeled Pittsburgh Compound B ([^{11}C]PIB); education
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Introduction

In vivo positron emission tomography (PET) studies have shown an increased uptake of the amyloid ligand ^{11}C-labeled Pittsburgh Compound B ([^{11}C]PIB) in Alzheimer's disease (AD) and mild cognitive impairment patients, especially in the frontal, parietal, and temporal cortices and in the posterior cingulate, indicating increased amyloid accumulation in these areas (Klunk *et al.*, 2004; Kemppainen *et al.*, 2006, 2007). Importantly, 20–30% of cognitively normal older individuals also display significant PIB uptake (Pike *et al.*, 2007; Morris *et al.*, 2010), which is consistent with the evidence that some older individuals who had intact cognition during their later life showed substantial numbers of amyloid-β (Aβ) plaques postmortem (Bennett *et al.*, 2006). A greater understanding of the factors associated with Aβ variability in the older population could have important consequences for disease prevention.

Several epidemiological studies have found a lower incidence of AD in highly educated populations, suggesting that education provides protection against

the disease (Stern *et al.*, 1994). This reduced risk for AD in highly educated individuals has been proposed to reflect an increased cognitive reserve that provides greater brain capacity to compensate for disruptions caused by disease pathology and can thus delay the clinical expression of AD (Stern, 2006). This cognitive-reserve hypothesis has been explored in relation to AD pathology (Rentz *et al.*, 2010; Vemuri *et al.*, 2012).

In contrast, individuals with greater early- and middle-life cognitive activity have shown lower [^{11}C]PIB uptake in a previous study (Landau *et al.*, 2012). Greater lifetime cognitive activity has been reported to forestall AD pathology, even in genetically susceptible individuals (Wirth *et al.*, 2014). These studies suggest that people with higher education, who might have more chance of lifetime cognitive activity, have greater inhibitory effects against Aβ deposition. Our objective was to examine the possible association of early-life education with [^{11}C]PIB uptake in later life stage of cognitively normal subjects. We hypothesize that cognitively normal and highly educated participants have lower [^{11}C]PIB uptake, indicating less pronounced pathological brain changes compared with less-educated participants with normal cognitive function. We investigated this hypothesis by performing [^{11}C]PIB-PET and neuropsychological testing in a sample of cognitively normal older participants. Aβ deposition in several cortical brain regions was examined in cognitively normal older participants with different education levels.

Materials and methods

Participants

Thirty cognitively normal older participants were recruited from the local area by poster advertisement. Sixteen participants received education for less than 13 years (low/middle-education group), and 14 had no less than 13 years of education (high-education group). Twelve years' education in Japan corresponds to the education from elementary school to high school, which was regarded as low to middle level of education in Japan. The inclusion criteria were an age of 55–79 years, a Mini-mental state examination (MMSE) score of 26 or higher (Folstein *et al.*, 1975), independent living in the community, normal performance on cognitive tests, and no major structural abnormalities or signs of major vascular pathology on magnetic resonance imaging (MRI). The exclusion criteria included major neurological, psychiatric, or medical illnesses; depression (assessed with the Geriatric Depression Scale) (Yesavage *et al.*, 1982–1983); the use of medications that affect cognition; and MRI contraindications. This study was approved by the institutional review boards of all of the participating institutions, and all participants gave written informed consent.

Neuropsychological testing

All of the participants completed an extensive neuropsychological battery, which was administered up to 1 month before the PET scan to screen for impaired cognition. They were assessed by the MMSE (Folstein *et al.*, 1975), the Alzheimer's Disease Assessment Scale-cognitive subscale (Rosen *et al.*, 1984), and the Raven's Colored Progressive Matrices (RCPM) (Raven, 1958) to measure general cognitive ability and intelligence. They were also assessed by the Wechsler Memory Scale-Revised (Wechsler, 1987) and the Rey Auditory Verbal Learning Test-Revised (Spreen and Strauss, 1991) to measure memory function and by the Frontal Assessment Battery (Dubois *et al.*, 2000) for frontal dysfunction. Attention and executive function were measured by the Trail Making Test (TMT) A and B (Partington and Leiter, 1949).

Probe synthesis

^{11}C-labeled Pittsburgh Compound B was synthesized by the reaction of 2-(40-aminophenyl)-6-hydroxybenzothiazole and [^{11}C]methyl triflate according to a previous method (Price *et al.*, 2005). The product had a radiochemical purity greater than 96.1%. The specific activity ranged from 36.7 to 135.2 GBq/mmol at the time of injection.

Positron emission tomography scanning

Positron emission tomography examinations were performed with a Biograph mCT (Siemens, Knoxville Healthcare/Molecular Imaging, TN, USA). This equipment provides a 40-slice CT, an axial field of view of 218 mm, a coincidence window of 4.1 ns, a timing resolution below 0.6 ns, and an energy window of 435–650 keV. Dynamic emission scan data were acquired in the three-dimensional mode for a period of 70 min. The participants were examined while they were resting in a supine position in a quiet room, and their heads were restrained with a band extending across the forehead that was attached to the headrest. An examiner carefully monitored head movement with laser beams during each scan, and corrections

were made when necessary. [^{11}C]PIB (644 ± 32 MBq) with 50 mL of saline was intravenously injected into the right antecubital vein via an infusion pump for 60 s. A sequence of 33 scans was acquired during 70 min (4 × 15 s, 8 × 30 s, 9 × 1 min, 2 × 3 min, and 10 × 5 min) after the [^{11}C]PIB injection. All data processing and image reconstruction including scatter correction were performed using the standard Siemens software.

Magnetic resonance image acquisition

All MRI examinations were performed on a 3.0-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased-array brain coil. High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient recalled sequence (repetition time = 12.8 ms, echo time = 2.6 ms, flip angle = 8°, field of view = 256 mm; 188 sections in the sagittal plane; acquisition matrix, 256 × 256; and acquired resolution, 1 mm × 1 mm × 1 mm).

Positron emission tomography data analysis

The regions that share a border with lower- or higher-binding structures are susceptible to partial-volume effects due to a blurring caused by the low resolution of PET (Hoffman *et al.*, 1979). Because the gray matter (GM), white matter (WM), and cerebrospinal fluid have different ^{11}C-PIB uptake patterns (Klunk *et al.*, 2004), all GM borders undergo partial-volume effects. Atrophy of a region that increases the amount of neighboring cerebrospinal fluid increases the partial-volume effects, and an effect of education on cortical volume has been reported (Arenaza-Urquijo *et al.*, 2013).

The [^{11}C]PIB-PET data were corrected for partial-volume effects with an algorithm that was implemented in the PMOD software package (PMOD V.3.3; PMOD Technologies GmbH, Adliswil, Switzerland). This correction is based on the assumption that WM uptake is homogeneous. All brain pixels are classified as either WM or GM and are sorted into respective segments. On the basis of these segments and the assumed PET resolution, the spill out from the WM to the GM can be estimated and subtracted. Similarly, the spill out from the GM to the surroundings can be estimated and compensated for. The result is a GM image with corrected activity values in all the pixels. This method was introduced by Müller-Gärtner *et al.* (Müller-Gärtner *et al.*, 1992). The corrections were performed using a point spread function, full-width-half-maximum of 4.0 mm × 4.0 mm × 4.0 mm, correction mode of GM spill out and spill in, WM estimation of regression of 0.95, and GM threshold of 0.5.

The radioactivity concentrations in six brain regions (the prefrontal cortex, lateral temporal cortex, parietal cortex, anterior cingulate cortex, posterior cingulate cortex, and cerebellum) were obtained with a template-based method for defining volumes of interest (Yasuno *et al.*, 2002). Regional time-activity data were analyzed with the Logan graphical method (Logan *et al.*, 1996) from 35 to 70 min of the PET data. The Logan graphical method has been shown to be stable, with a high test–retest reliability (Price *et al.*, 2005) and sensitivity to small changes in ^{11}C-PIB (Lopresti *et al.*, 2005). This method yields binding potential (BP) estimates relative to the non-displaceable (ND) binding, which is denoted by BP_{ND} (Innis *et al.*, 2007).

Analysis methods that used 90 min of PIB-PET data performed better compared with when 60 min was used, but 60 min of PET data also yielded useful data, as judged by the evaluation criteria (Lopresti *et al.*, 2005). Because of considerations of the fatigue of the subjects and the maintenance of the reliability of the analysis, we used the 35–70 min PET data for this analysis.

A voxel-based BP_{ND} was estimated from the [^{11}C]PIB-PET data with a Logan plot graphical analysis, with the cerebellum as the reference region in the PMOD software package. The spatial preprocessing of maps was performed using statistical parametric mapping (SPM, Wellcome Institute of Neurology, University College London, UK). Each T1-weighted MRI scan was coregistered to each PET image, and the spatial normalization of the MRI images to the SPM8 T1-MRI template was applied to the PET images. The normalized BP images were smoothed with a Gaussian filter to 10 mm full-width-half-maximum. We performed a voxel-based analysis of covariance (ANCOVA) on the BP_{ND} images between the low/middle- and high-education groups, while adjusting for differences in age, sex, and RCPM scores (a measure of general intelligence) as possible confounding factors.

Statistical analysis

Statistical analysis was performed with SPSS for Windows 22.0 (IBM Japan, Tokyo, Japan). Regional BP values of the two groups were compared using repeated measures ANCOVA with a Greenhouse–Geisser correction, using age, sex, and RCPM scores as covariates. A follow-up ANCOVA with age, sex, and RCPM score as covariates was performed on the

BP_{ND} values of each volumes of interest. Global cortical mean BP_{ND} values were also compared between groups with ANCOVA using age, sex, and RCPM score as covariates. The correlation between the global cortical mean BP_{ND} values and the duration of education for all of the subjects was evaluated with a Spearman's ρ test. All of the statistical tests were two-tailed and considered significant at $p < 0.05$.

Analysis of the parametric BP images with SPM8 was performed to examine the differences in BP_{ND} between the groups. The statistical test results with an uncorrected p level of 0.001 were considered significant. Clusters of at least 50 contiguous significant voxels were interpreted as significant sites.

Results

Demographic and clinical data

Table 1 summarizes the demographic and clinical characteristics of the participants in the low/middle- and high-education groups. They did not differ significantly in age. The percentage of males was higher in the highly educated group, but the difference in the percentage was not significant between the groups. As for the cognitive functions measured with the MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale, RCPM, and several neuropsychological tests, neither of the groups showed any abnormalities, and all of the scores were within normal ranges. There were no significant between-group differences in the scores of these tests except for the RCPM, which was higher in the highly educated group.

Differences in the Pittsburgh Compound B-binding potential values between the low/middle- and high-education groups

Table 2 shows the PIB-BP_{ND} values between the low/middle- and high-education groups. An ANCOVA of the BP_{ND} values for these groups with age, sex, and RCPM score as covariates revealed a significant main effect of education on the PIB-BP_{ND} values. Follow-up

Table 1 Demographic statistics and neuropsychological performances of the low/middle- and high-education groups

Characteristic/test	Low/middle education	High education	t_{28} or χ^2	p
No.	16	14		
Sex M/F	7/9	11/3	3.77	0.05
Age, y	70.3 ± 5.6	68.7 ± 8.2	0.60	0.55
Education, y	11.4 ± 1.6	16.1 ± 2.0	6.95	0.0001[h]
MMSE[a]	29.3 ± 1.2	29.6 ± 0.6	1.07	0.29
ADAS-C[b]	3.6 ± 1.3	3.7 ± 1.7	0.12	0.90
RCPM[c]	32.5 ± 2.6	34.4 ± 2.2	2.18	0.04[h]
GDS[d]	2.6 ± 2.8	3.8 ± 3.6	1.02	0.32
Neuropsychological tests				
WMS-R[e]				
Verbal memory index	108.3 ± 9.2	113.5 ± 5.7	1.82	0.08
Visual memory index	106.7 ± 11.4	109.1 ± 9.8	0.61	0.55
General memory index	108.6 ± 9.8	113.4 ± 6.6	1.55	0.13
Attention index	104.8 ± 13.1	108.6 ± 13.2	0.80	0.43
Delayed memory index	107.5 ± 9.4	111.9 ± 7.3	1.43	0.17
RAVLT[f]				
Maximum of the correct immediate recall	12.4 ± 1.3	12.9 ± 1.1	1.26	0.22
Delayed recall	10.5 ± 2.1	11.1 ± 2.1	0.83	0.41
Delayed recognition	47.2 ± 3.2	48.1 ± 1.9	0.91	0.37
FAB[g]	17.2 ± 0.8	17.3 ± 0.9	0.32	0.75
Trail making test (second)				
A	36.8 ± 15.4	36.6 ± 10.6	0.02	0.98
B	93.6 ± 36.2	92.4 ± 23.2	0.11	0.92

Data are mean ± standard deviation (SD).
[a]Mini-mental state examination.
[b]Alzheimer's Disease Assessment Scale-cognitive subscale.
[c]Raven's Colored Progressive Matrices.
[d]Geriatric Depression Scale.
[e]Wechsler Memory Scale-Revised.
[f]Rey Auditory Verbal Learning Test-Revised.
[g]Frontal Assessment Battery.
[h]$p < 0.05$.

Table 2 Comparison of binding potential (BP_{ND}) values between the groups with low/middle and high education

Region	BP_{ND} values (mean ± SD)[a,b]		Analysis of covariance	
	Low/middle education ($n = 16$)	High education ($n = 14$)	F ($df = 1, 25$)	p
Prefrontal cortex	0.24 ± 0.18	0.11 ± 0.19	3.40	0.08
Lateral temporal cortex	0.12 ± 0.16	−0.03 ± 0.16	5.64	0.03[c]
Parietal cortex	0.19 ± 0.18	0.06 ± 0.18	3.40	0.08
Anterior cingulate cortex	0.30 ± 0.18	0.14 ± 0.18	4.82	0.04[c]
Posterior cingulate cortex	0.30 ± 0.18	0.16 ± 0.18	3.87	0.06
Global cortical mean	0.23 ± 0.16	0.09 ± 0.16	4.90	0.04[c]

[a]BP_{ND} values were adjusted for age and sex.
[b]Repeated measures of analysis of covariance with age, sex, and RCPM score as covariates revealed a significant main effect of education (Regions: $F = 0.73$, $df = 2.3$, 58.2, $p = 0.51$; region × education: $F = 0.16$, $df = 2.3$, 58.2, $p = 0.88$; education: $F = 4.90$, $df = 1$, 25, $p = 0.04$).
[c]$p < 0.05$

analysis revealed that the BP_{ND} values of the low/middle-education group were significantly higher in the lateral temporal and anterior cingulate cortices. The BP_{ND} values of the low/middle-education group in other regions showed a trend toward an increase compared with the high-education group ($p < 0.1$). The global mean BP_{ND} values were significantly higher in the low/middle-education group than the high-education group (Table 2, Figure 1(a)). Four of the "low/middle education" group showed relatively high BP values (>0.3), which were high enough to suggest that the PIB binding is positive. However, when we removed these subjects from the data, the low/middle-education group remained to show higher global mean BP_{ND} values ($F_{1, 21} = 8.59$, $p = 0.008$). When we applied a nonparametric analysis with the Mann–Whitney U test, the result was not changed ($Z = 2.99$, $p = 0.002$). There was a significant correlation between the duration of education and the global mean BP_{ND} values for all the subjects ($r = -0.58$, $p = 0.001$; Figure 1(b)).

In the voxel-based ANCOVA of the PIB-BP_{ND} values, the low/middle-education group showed higher BP_{ND} values in the broad cortical areas shown in Table 3 and Figure 2. There were no significantly lower BP_{ND} values in any region in the low/middle-education group.

Discussion

This study demonstrated significantly higher cortical PIB-BP_{ND} in the cognitively normal participants with low/middle levels of education compared with those with high levels of education. Neither group showed a significant difference in the cognitive measurements, except for the RCPM score, which is a measure of

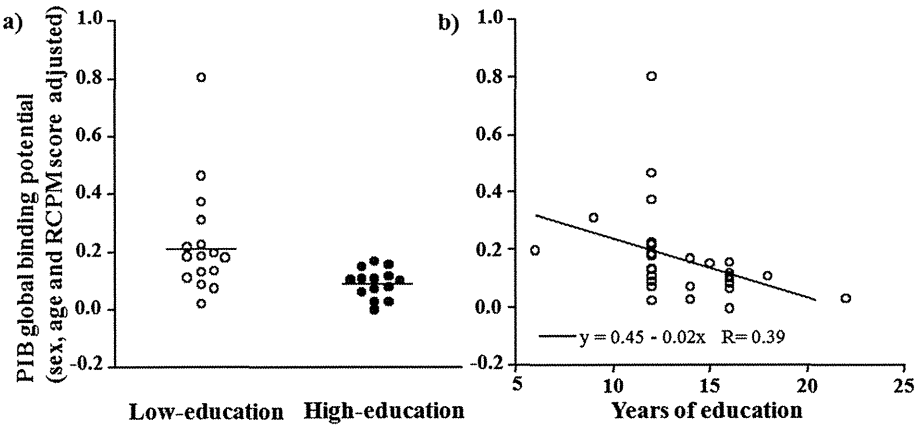

Figure 1 (a) The scatter plot of global cortical mean Pittsburgh Compound B-binding potential (PIB-BP_{ND}) of the participants in the low/middle- and high-education groups, and (b) the plot between PIB-BP_{ND} and the duration of education for all subjects. The PIB-BP_{ND} values were adjusted for the variables of age, sex, and Raven's Colored Progressive Matrices (RCPM) score.

Table 3 Regions showing significant difference in BP_{ND} between low/middle- and high-education groups in the voxel-based analysis

Comparison	Region	BA	MNI coordinates (*x*, *y*, *z*)	voxels	*t*-value
Education high > education low/middle	None				
Education high < education low/middle	R supramarginal gyrus	40	50, −36, 32	647	4.89
	L lingual gyrus	18	−16, −78, 2	462	4.85
	L middle frontal gyrus	11	−22, 38, −10	129	4.56
	R putamen	—	32, −18, −4	458	4.48
	R inferior frontal gyrus	47	44, 20, 20	56	4.25
	L superior parietal gyrus	7	−28, −44, 42	59	4.13
	L hippocampus	—	−40, −20, −10	217	4.04
	R middle frontal gyrus	11	18, 44, −14	82	4.04
	L inferior parietal gyrus	40	−48, −20, 24	170	4.03
	R inferior parietal gyrus	40	42, −28, 52	132	3.93
	R thalamus	—	24, −32, 2	75	3.85
	L middle temporal gyrus	37	−40, −64, 0	83	3.81
	L putamen	—	−30, 6, −2	74	3.80

BP_{ND}, binding potential; MNI, Montreal Neurological Institute; BA, Brodmann area; R, right; L, left.

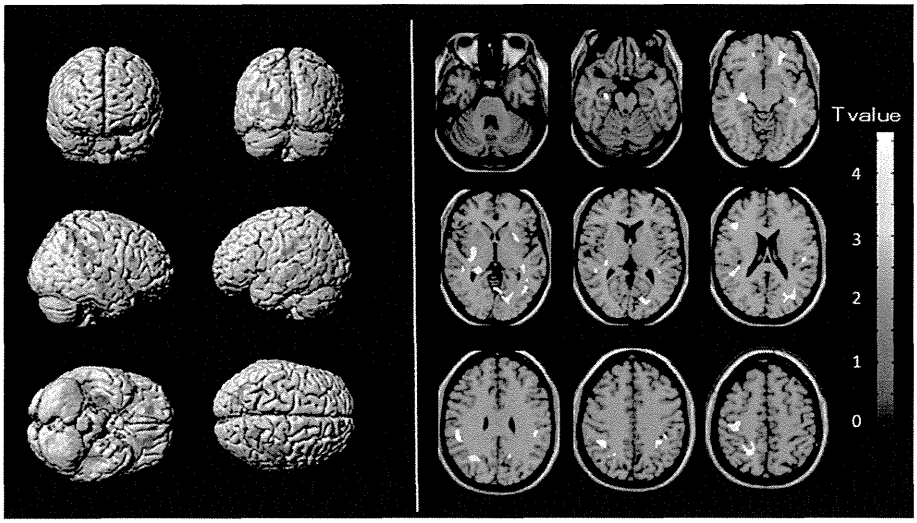

Figure 2 Images of voxel-based maps showing greater Pittsburgh Compound B-binding potential (BP_{ND}) values in the low/middle-education group compared with the highly educated group ($p < 0.001$, uncorrected, extent threshold >50 voxels). Rendered images are on the left, and axial images are on the right. The Montreal Neurological Institute coordinates of the areas showing significantly higher BP_{ND} values in the low/middle-education group compared with the high-educated group are shown in Table 3.

general intelligence. We found a higher RCPM score in the highly educated group, and the difference in the sex ratio between the groups was nearly significant. However, the finding of higher cortical PIB-BP_{ND} values in the participants with less education was not affected by the inclusion of the possible confounding variables of sex, age, or RCPM scores. In addition, we found a significant correlation between the duration of education and PIB binding in all of the subjects.

The lower incidence of AD in highly educated populations has been shown in several epidemiological studies (Stern *et al.*, 1994), but the protective mechanism of education against the disease is still unclear. Our findings indicated reduced amyloid pathology in highly educated and cognitively normal participants, which leads to the proposal that early-life education is associated with PIB, suggesting that it may have an inhibitory effect on AD pathology. Our study analyzes the effects of education on the development of pathological changes in the brain during the presymptomatic phase of AD.

One explanation for the negative relationship between early-life education and AD pathology was that it was induced from psychosocial factors, such as socioeconomic and lifestyle differences. For example, higher education is often associated with a healthier

lifestyle, less disease, and lower exposure to toxic factors due to a better environment. These may contribute to the differences between the educational groups, as has been suggested for heart disease mortality (Springer *et al.*, 2005). Another possibility is that lifelong mental stimulation results from education. We expected that people with higher education had more knowledge and opportunities for various experiences. They could have an inquiring mind and have a greater chance for developing their imagination and intelligence. As a result, they may have lifelong cognitive stimulation that induces high neural activity.

Recent *in vitro* studies in animals and humans have indicated that neural activity regulates the secretion of Aβ (Kamenetz *et al.*, 2003; Cirrito *et al.*, 2005; Brody *et al.*, 2008; Bero *et al.*, 2011). Although it is difficult to verify the association between increased neural activation and Aβ deposition in humans, individuals with greater early- and middle-life cognitive activity have been shown to have lower [^{11}C]PIB uptake in a previous study (Landau *et al.*, 2012). Individuals who participate in a variety of cognitively stimulating activities during their lifespan may develop more efficient neural processing that results in less Aβ deposition (Jagust and Mormino, 2011). Supporting this idea, transgenic Aβ-expressing mice that were exposed to enriched environments deposit less Aβ than control animals (Lazarov *et al.*, 2005; Costa *et al.*, 2007).

Our study had some limitations. Firstly, in contrast to the epidemiologic data rested on large population studies, our data of 30 individuals recruited from the local area by poster advertisement are not based on the random sampling selection. Secondly, this was a cross-sectional survey and not a longitudinal follow-up study. Thirdly, some of the subjects in the low/middle-education group showed high BP_{ND} values and could not be regarded as healthy subjects, even though they were cognitively normal. It would be premature to draw definitive conclusions from this analysis. However, in spite of these shortcomings, the current data would be useful as pilot for future studies in a larger, more representative cohort.

The present study possibly extends previous findings of a lower incidence of AD in highly educated populations, suggesting that education provides protection against the disease. Our findings are not opposed to the brain reserve hypothesis, which implies that people with higher education have a greater reserve capacity. People with more education might be prone to have a greater inhibitory effect against Aβ deposition before the preclinical stage and, at the same time, have greater reserve capacity: requiring greater pathological changes for dementia to manifest.

Conflict of interest

None declared.

Key points

- Reduced amyloid pathology in highly educated, cognitively normal subjects.
- Early-life education has a negative association with AD pathology in the later stage of life.

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References

Arenaza-Urquijo EM, Landeau B, La Joie R, *et al.* 2013. Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *Neuroimage* **83**: 450–457.

Bennett DA, Schneider JA, Arvanitakis Z, *et al.* 2006. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology* **66**: 1837–1844.

Bero AW, Yan P, Roh JH, *et al.* 2011. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. *Nat Neurosci* **14**: 750–756.

Brody DL, Magnoni S, Schwetye KE, *et al.* 2008. Amyloid-beta dynamics correlate with neurological status in the injured human brain. *Science* **321**: 1221–1224.

Cirrito JR, Yamada KA, Finn MB, *et al.* 2005 Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron* **48**: 913–922.

Costa DA, Cracchiolo JR, Bachstetter AD, *et al.* 2007. Enrichment improves cognition in AD mice by amyloid-related and unrelated mechanisms. *Neurobiol Aging* **28**: 831–844.

Dubois B, Slachevsky A, Litvan I, Pillon B. 2000. The FAB: a Frontal Assessment Battery at bedside. *Neurology* **55**: 1621–1626.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–198.

Hoffman EJ, Huang SC, Phelps ME. 1979. Quantitation in positron emission computed tomography: 1. Effect of object size. *J Comput Assist Tomogr* **3**: 299–308.

Innis RB, Cunningham VJ, Delforge J, *et al.* 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* **27**: 1533–1539.

Jagust WJ, Mormino EC. 2011. Lifespan brain activity, β-amyloid, and Alzheimer's disease. *Trends Cogn Sci* **15**: 520–526.

Kamenetz F, Tomita T, Hsieh H, *et al.* 2003. APP processing and synaptic function. *Neuron* **37**: 925–937.

Kemppainen NM, Aalto S, Wilson IA, *et al.* 2006. Voxel-based analysis of PET amyloid ligand [^{11}C]PIB uptake in Alzheimer disease. *Neurology* **67**: 1575–1580.

Kemppainen NM, Aalto S, Wilson IA, *et al.* 2007. PET amyloid ligand [^{11}C]PIB uptake is increased in mild cognitive impairment. *Neurology* **68**: 1603–1606.

Klunk WE, Engler H, Nordberg A, *et al.* 2004. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* **55**: 306–319.

Landau SM, Marks SM, Mormino EC, *et al.* 2012. Association of lifetime cognitive engagement and low β-amyloid deposition. *Arch Neurol* **69**: 623–629.

Lazarov O, Robinson J, Tang YP, *et al.* 2005. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* **120**: 701–713.

Logan J, Fowler JS, Volkow ND, *et al.* 1996. Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab* **16**: 834–840.

Lopresti BJ, Klunk WE, Mathis CA, *et al.* 2005. Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. *J Nucl Med* **46**: 1959–1972.

Müller-Gärtner HW, Links JM, Prince JL, *et al.* 1992. Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI-based correction for partial volume effects. *J Cereb Blood Flow Metab* **12**: 571–583.

Morris JC, Roe CM, Xiong C, *et al.* 2010. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* **67**: 122–131.

Partington JE, Leiter RG. 1949. Partington's pathway test. *Psychol Serv Cent Bull* **1**: 9–20.

Pike KE, Savage G, Villemagne VL, *et al.* 2007. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* **130**: 2837–2844.

Price JC, Klunk WE, Lopresti BJ, *et al.* 2005. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *J Cereb Blood Flow Metab* **25**: 1528–1547.

Raven JC. 1958. Guide to the Standard Progressive Matrices. HK Lewis: London.

Rentz DM, Locascio JJ, Becker JA, *et al.* 2010. Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol* **67**: 353–364.

Rosen WG, Mohs RC, Davis KL. 1984. A new rating scale for Alzheimer's disease. *Am J Psychiatry* **141**: 1356–1364.

Spreen O, Strauss E. 1991. A Conpendium of Neuropsychological Tests. Oxford University Press: Oxford.

Springer MV, McIntosh AR, Winocur G, Grady CL. 2005. The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology* **19**: 181–192.

Stern Y. 2006. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord* **20**: S69-74.

Stern Y, Gurland B, Tatemichi TK, *et al.* 1994. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**: 1004–1010.

Vemuri P, Lesnick TG, Przybelski SA, *et al.* 2012. Effect of lifestyle activities on Alzheimer disease biomarkers and cognition. *Ann Neurol* **72**: 730–738.

Wechsler D. 1987. Wechsler Memory Scale-Revised. Harcourt Brace Jovanovich: San Antonio.

Wirth M, Villeneuve S, La Joie R, Marks SM, Jagust WJ 2014 Gene-environment interactions: lifetime cognitive activity, APOE genotype, and β-amyloid burden. *J Neurosci* **34**: 8612–8617.

Yasuno F, Hasnine AH, Suhara T, *et al.* 2002. Template-based method for multiple volumes of interest of human brain PET images. *Neuroimage* **16**: 577–586.

Yesavage JA, Brink TL, Rose TL, *et al.* 1982–1983. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17**: 37–49.

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ANNALS OF GENERAL PSYCHIATRY

CASE REPORT Open Access

Paliperidone extended release for the treatment of pediatric and adolescent patients with Tourette's disorder

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Abstract

Objective: A subgroup of patients with Tourette's disorder (TD) has symptoms refractory to haloperidol, a standard therapeutic drug for TD.

Methods: We report on three cases of pediatric and adolescent patients who were treated with paliperidone extended release.

Results: In two cases, TD symptoms were remarkably improved by switching from haloperidol to paliperidone extended release, and in another case, paliperidone extended release showed significant efficacy in treating TD symptoms as the first-line drug. In all cases, no significant adverse side effects were detected.

Conclusion: Paliperidone extended release may be a strong candidate for the treatment of pediatric and adolescent patients with TD.

Keywords: Tourette's disorder, Paliperidone extended release, Haloperidol, Tics

Introduction

Tourette's disorder (TD) is a neurodevelopmental disorder commonly associated with the presence of multiple vocal and/or motor tics. The onset of TD occurs in childhood and the prevalence is higher in males than in females (4.3: 1) [1,2]. Of school-aged children, 6%–20% experience transient tics and 0.5%–1% suffer from chronic tics or TD [3]. TD usually has a familial component [2]. The majority of patients with TD also meet the criteria for one or more comorbid psychiatric disorders, including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), mood disorder, and non-OCD anxiety disorder [4]. Since there are several biological hypotheses relating to TD that highlight dopaminergic function, typical antipsychotics such as haloperidol and pimozide have been prescribed to control tic symptoms [5]. More recently, clinical opportunities for prescribing atypical antipsychotics such as risperidone, quetiapine, aripiprazole, and olanzapine have increased owing to the enhanced efficacy and more tolerable side effect profiles relative to classical antipsychotics [1,6-8]. Considering all antipsychotics, risperidone is commonly recommended by experts [9,10].

This report focuses on the utilization of the atypical antipsychotic, paliperidone extended release (ER), which chemically is a major active metabolite of risperidone (9-hydroxyrisperidone), in the treatment of child and adolescent patients with TD since our survey of the literature has failed to identify any current reports related to its use in this setting. The three cases showed reductions in TD symptom severity over a relatively short time period and an improvement in the Yale Global Tic Severity Scale (YGTSS) [11], a clinician-rated, semistructured interview useful for determining both the effects of treatment as well as providing an assessment of tic severity (0–50 scale range, impairment score not included). Motor and phonic tics were rated separately according to number, frequency, intensity, complexity, and interference.

According to the World Medical Association Declaration of Helsinki, a statement of ethical principles for medical research in human patients, we provided

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patients and patients' parents with thorough monitoring information and any serious adverse events.

Case presentation

Case A

Patient A is a 10-year-old boy who developed facial motor tics such as blinking and grimacing at 8 years of age. He also began to express involuntary utterances consisting of the vowel sound 'a' and excessive shoulder shrugging when he was 9 years old. At the age of 10, the abnormal 'a' vocalization was replaced with very loud snoring. Subsequently, he began to display involuntary coprolalia using words such as 'kill' and 'die.' Treatment with haloperidol (1.5 mg/day) failed to improve the tic symptoms while being followed at a local clinic. Since the tics had a significant negative impact on his activities of daily living and social relationships, he was referred to our hospital when he was 10 years old. TD was diagnosed in accordance with DSM-IV-TR and his YGTSS was 27. He did not have ADHD, OCD, or other behavioral or psychiatric disorders. He was prescribed with 3 mg of paliperidone ER to improve tic symptoms and scheduled for weekly visits to our hospital to monitor side effects. One week after initiation of paliperidone ER, the occurrence of coprolalia had dramatically improved, although he still displayed motor and vocal tics (YGTSS 20), which were gradually improved with few side effects. Within 2 months, his vocal tic symptoms had nearly disappeared, but slight shoulder shrugging remained (YGTSS 7).

Case B

Patient B is an 11-year-old boy who developed motor tics such as blinking and coughing at 9 years old. He began to express an involuntary vocal utterance as a very loud 'a' sound at the age of 11. Since both the frequency and severity of these motor and vocal tics worsened, he was referred to our hospital. His was diagnosed with TD in accordance with DSM-IV-TR and his YGTSS was 21. He did not have ADHD, OCD, or other behavioral or psychiatric disorders. First, he was prescribed with 3 mg/day of paliperidone ER to improve the tic symptoms. While the volume of his vocal tics became lower after three weeks of paliperidone ER treatment, his overall tic symptoms were not improved (YGTSS 17). After having been on 3 mg/day of paliperidone ER for 6 weeks, his dosage was increased to 6 mg/day. Two weeks after initiating the 6 mg/day paliperidone ER treatment, both the motor and vocal tic symptoms had substantially improved with few side effects (YGTSS 7).

Case C

Patient C is 13-year-old boy who developed motor tics such as violent neck shaking, repeated jumping, and sniffing as well as vocal tics beginning at 8 years of age. He visited our hospital when he was 11 years old and was diagnosed with TS in accordance with DSM-IV-TR and his YGTSS was 18. While there was a family history of TD, neither ADHD, OCD, nor other behavioral or psychiatric disorders were identified. He had been treated with haloperidol (1.5 mg/day) for approximately 2 years and showed only mild improvement while the presence of drowsiness prevented further dosage titration. He was prescribed with 3 mg/day of paliperidone ER and showed no improvement in his tic symptoms over the course of 3 weeks following initiation of therapy (YGTSS 16). Subsequently, the dosage of paliperidone ER was increased to 6 mg/day. After 5 weeks of higher dosage of paliperidone ER, he did experience mild drowsiness but significant improvement of the tic symptoms was observed (YGTSS 6). Due to the presence of the mild drowsiness, the dosage of paliperidone ER was then reduced to 3 mg/day and, despite this reduction, his tic symptoms did not recur over the following 4 months (YGTSS 7).

Discussion

To the best of our knowledge, only a single case study has reported beneficial effects of paliperidone ER for the treatment of an adult patient who was diagnosed with TD and comorbid schizophrenia [12]. The cases presented here are the first reports showing the therapeutic effects of paliperidone ER in treating child and adolescent patients with TD.

While the exact pathobiology of TD remains unknown, several hypotheses have been proposed. Dysfunction in the cortico-striatal-thalamo-cortical (CSTC) circuits has been suggested as a potential cause of TD [13]. Previous studies using single-photon emission computed tomography (SPECT) have suggested higher levels of dopamine transporter binding in the caudate and putamen nuclei in TD patients as compared to healthy controls [14]. Furthermore, greater putamen dopamine release was observed in TD in comparison to healthy controls using positron emission tomography (PET) [15]. These findings are supportive of abnormalities in dopaminergic function as potential participants in the pathophysiology of TD. Therefore, typical or atypical antipsychotics, which generally block dopaminergic signaling, have been prescribed to control its tic symptoms. Of all antipsychotics, currently risperidone is recommended by the experts to treat tic symptoms [9,10]. Risperidone has potent dopamine-2 (D_2) and 5-hydroxytryptamine (5-HT2A) receptor blocking properties, and it has been proven to be as effective for the treatment of TD as haloperidol and relatively safer compared to haloperidol in terms of side effects (e.g., high frequency of extrapyramidal symptoms by haloperidol) [16,17]. While the

major anti-tic efficacy of risperidone is probably due to the blocking of dopaminergic neurotransmission, the serotonergic action might give additional effects by indirectly attenuating mesolimbic and/or mesocortical dopaminergic pathways [18]. Therefore, risperidone could be a better pharmacotherapeutic agent for the treatment of TD than other typical antipsychotics such as haloperidol. However, resperidone also has its own problematic side effects including oversedation and weight gain, and here we would like to suggest the possibility that paliperidone ER, the extended-release form of the major metabolite of risperidone, could be used to avoid these adverse events especially since blood concentration of paliperidone ER is relatively stable [19] leading to less daytime somnolence [20] and it can produce fewer extrapyramidal symptoms as compared to risperidone [21]. As daytime somnolence and extrapyramidal symptoms substantially disturb children's life; study, exercise, friendship, and so on, paliperidone ER may serve as an advantageous pharmacotherapy for the treatment of child and adolescent TD.

Conclusion

These cases suggest that paliperidone ER might serve as an efficacious therapy in child and adolescent patients with TD and present few side effects. Further information and details provided by studies using larger sample sizes are needed to validate the apparent efficacy, safety, and tolerability of paliperidone ER in the treatment of child and adolescent patients with TD.

Consent

Written informed consent was obtained from the patient's parents for the publication of this report and any accompanying images.

Abbreviations

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TD: Tourette's disorder; YGTSS: Yale Global Tic Severity Scale.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KY was involved in the collection of the data and wrote the first draft of the manuscript. MM, TO, JI and TK supervised the entire project and was critically involved in the design, and contributed to the editing of the final manuscript. All authors have read and approved the final manuscript.

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References

1. Stephens RJ, Bassel C, Sandor P: **Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome–a pilot study.** *J Child Adolesc Psychopharmacol* 2004, **14**(2):255–266.
2. Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P: **An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries.** *Dev Med Child Neurol* 2000, **42**(7):436–447.
3. Swain JE, Scahill L, Lombroso PJ, King RA, Leckman JF: **Tourette syndrome and tic disorders: a decade of progress.** *J Am Acad Child Adolesc Psychiatry* 2007, **46**(8):947–968.
4. Coffey BJ, Biederman J, Spencer T, Geller DA, Faraone SV, Bellordre CA: **Informativeness of structured diagnostic interviews in the identification of Tourette's disorder in referred youth.** *J Nerv Ment Dis* 2000, **188**(9):583–588.
5. Rampello L, Alvano A, Battaglia G, Bruno V, Raffaele R, Nicoletti F: **Tic disorders: from pathophysiology to treatment.** *J Neurol* 2006, **253**(1):1–15.
6. Gilbert DL, Batterson JR, Sethuraman G, Sallee FR: **Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial.** *J Am Acad Child Adolesc Psychiatry* 2004, **43**(2):206–214.
7. Copur M, Arpaci B, Demir T, Narin H: **Clinical effectiveness of quetiapine in children and adolescents with Tourette's syndrome: a retrospective case-note survey.** *Clin Drug Investig* 2007, **27**(2):123–130.
8. Lyon GJ, Samar S, Jummani R, Hirsch S, Spirgel A, Goldman R, Coffey BJ: **Aripiprazole in children and adolescents with Tourette's disorder: an open-label safety and tolerability study.** *J Child Adolesc Psychopharmacol* 2009, **19**(6):623–633.
9. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, Strand G, Stern JS, Termine C, Hoekstra PJ: **European clinical guidelines for Tourette syndrome and other tic disorders: part II: pharmacological treatment.** *Eur Child Adolesc Psychiatry* 2011, **20**(4):173–196.
10. Scahill L, Erenberg G, Berlin CM Jr, Budman C, Coffey BJ, Jankovic J, Kiessling L, King RA, Kurlan R, Lang A, Mink J, Murphy T, Zinner S, Walkup J, Tourette Syndrome Association Medical Advisory Board: Practice Committee: **Contemporary assessment and pharmacotherapy of Tourette syndrome.** *NeuroRx* 2006, **3**(2):192–206.
11. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ: **The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity.** *J Am Acad Child Adolesc Psychiatry* 1989, **28**(4):566–573.
12. Guan CH, Tsai SJ: **Paliperidone in the treatment of Tourette's syndrome with comorbid schizophrenia.** *Psychiatry Clin Neurosci* 2013, **67**(2):128.
13. Mink JW: **Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis.** *Pediatr Neurol* 2001, **25**(3):190–198.
14. Serra-Mestres J, Ring HA, Costa DC, Gacinovic S, Walker Z, Lees AJ, Robertson MM, Trimble MR: **Dopamine transporter binding in Gilles de la Tourette syndrome: a [123I]FP-CIT/SPECT study.** *Acta Psychiatr Scand* 2004, **109**(2):140–146.
15. Singer HS, Szymanski S, Giuliano J, Yokoi F, Dogan AS, Brasic JR, Zhou Y, Grace AA, Wong DF: **Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET.** *Am J Psychiatry* 2002, **159**(8):1329–1336.
16. Bruggeman R, van der Linden C, Buitelaar JK, Gericke GS, Hawkridge SM, Temlett JA: **Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study.** *J Clin Psychiatry* 2001, **62**(1):50–56.
17. Dion Y, Annable L, Sandor P, Chouinard G: **Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial.** *J Clin Psychopharmacol* 2002, **22**(1):31–39.
18. Kapur S, Remington G: **Serotonin-dopamine interaction and its relevance to schizophrenia.** *Am J Psychiatry* 1996, **153**(4):466–476.
19. Owen RT: **Extended-release paliperidone: efficacy, safety and tolerability profile of a new atypical antipsychotic.** *Drugs Today (Barc)* 2007, **43**(4):249–258.
20. Luthringer R, Staner L, Noel N, Muzet M, Gassmann-Mayer C, Talluri K, Cleton A, Eerdekens M, Battisti WP, Palumbo JM: **A double-blind, placebo-controlled, randomized study evaluating the effect of paliperidone extended-release tablets on sleep architecture in patients with schizophrenia.** *Int Clin Psychopharmacol* 2007, **22**(5):299–308.
21. Suzuki H, Gen K, Inoue Y, Hibino H, Mikami A, Matsumoto H, Mikami K: **The influence of switching from risperidone to paliperidone on the extrapyramidal symptoms and cognitive function in elderly patients with schizophrenia: a preliminary open-label trial.** *Int J Psychiatry Clin Pract* 2014, **18**(1):58–62.

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