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ARTICLE

In vivo imaging of dopamine D1 receptor and activated microglia in attention-deficit/hyperactivity disorder: a positron emission tomography study

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Abstract

Alterations in the cortical dopamine system and microglial activation have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), one of neurodevelopmental disorders that can be conventionally treated with a dopamine enhancer (methylphenidate) albeit unsatisfactorily. Here, we investigated the contributions of the dopamine D1 receptor (D1R) and activated microglia and their interactions to the clinical severities in ADHD individuals using positron emission tomography (PET). Twenty-four psychotropic-naïve ADHD individuals and 24 age- and sex-matched typically developing (TD) subjects underwent PET measurements with [^{11}C]SCH23390 for the D1R and [^{11}C](*R*)PK11195 for activated microglia as well as assessments of clinical symptoms and cognitive functions. The ADHD individuals showed decreased D1R in the anterior cingulate cortex (ACC) and increased activated microglia in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) compared with the TD subjects. The decreased D1R in the ACC was associated with severe hyperactivity in the participants with ADHD. Microglial activation in the DLPFC were associated with deficits in processing speed and attentional ability, and that in the OFC was correlated with lower processing speed in the ADHD individuals. Furthermore, positive correlations between the D1R and activated microglia in both the DLPFC and the OFC were found to be significantly specific to the ADHD group and not to the TD group. The current findings suggest that microglial activation and the D1R reduction as well as their aberrant interactions underpin the neurophysiological mechanism of ADHD and indicate these biomolecular changes as a novel therapeutic target.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder characterized by inattentiveness and hyperactivity/impulsivity [1], as the worldwide prevalence is above 5% [2]. Because methylphenidate shows the highest effect size for ADHD (above 0.7) [3] but hampers physical growth and cardiovascular functions [4–6] with a low tolerability (40% dropout) [3, 7, 8], an alternative treatment has been expected.

The pharmacological effects of methylphenidate, inhibiting dopamine, and norepinephrine transporters, suggest the involvements of dopamine and norepinephrine systems in the pathophysiology of ADHD, with enhancing effects on cognitive functions through the dopamine D1 receptor (D1R) in animal studies [9–12]. Meta-analyses showed significant associations between ADHD and polymorphisms in the dopamine D2, D4, and D5 receptors and

transporters but not in norepinephrine receptors (i.e., alpha 2a-adrenergic receptors) or taransporters [13, 14]. In addition, the D1R polymorphism was also reported to be associated with ADHD [15, 16]. Positron emission tomography (PET) studies in typically developing (TD) human subjects showed the associations between the D1R and certain cognitive functions, such as working memory, response inhibition, and reward processes, which were affected in ADHD [17–22]. Moreover, downregulated D1-like receptors, indicating D1 and D5 receptors, in the anterior cingulate cortex (ACC) was observed in an ADHD model animal [23]. Because several lines of previous studies have emphasized a role of the D1R in the ADHD pathophysiology, the direct evaluation of the D1R in individuals with ADHD might provide evidence for a novel pharmacological target.

Polymorphisms of interleukin-6 (IL-6), IL-16, and tumor necrosis factor alpha (TNF-α) in individuals with ADHD were different from those in TD subjects and were associated with symptom severities and cognitive impairments [24, 25]. Drug-naïve individuals with ADHD showed higher serum levels of IL-6 and IL-10 than TD subjects [26], while medicated individuals with ADHD showed lower serum levels of IL-6, IL-13, and interferon gamma than drug-naïve ones [27, 28]. The levels of IL-6, IL-13, and TNF-α were associated with inattention and impulsivity in individuals with ADHD [29]. Although these cytokine studies suggested the involvement of neuroinflammation in ADHD, only one study without control group reported cytokine levels in cerebrospinal fluid in individuals with ADHD [30]. In the neuroinflammatory processes of central nervous system, activated microglia play an important role in interactions with various cytokines [31]. Therefore, it is easy to speculate that microglia engage in the development of neuroinflammation in ADHD. Experimentally, methylphenidate improves cognitive impairments by modifying microglial activation and cytokines in animal studies [32–34]. In a randomized, double blind, placebo-controlled clinical trial, the efficacy of anti-inflammatory treatments was found to exist in individuals with ADHD [35, 36]. Therefore, the clarification of possible associations between microglial activation and ADHD might indicate a new treatment strategy, i.e., targeting neuroinflammation.

Previous neuroimaging studies have shown several brain regions implicated in the cognitive deficits of ADHD: attention and the dorsolateral prefrontal cortex (DLPFC), dorsal striatum, thalamus, and frontal eye field [37]; response inhibition and the DLPFC, ACC, thalamus, and supplementary motor area; [37, 38] working memory and the DLPFC and orbitofrontal cortex (OFC) [38]; and reward processing and the OFC, nucleus accumbens, and ventral tegmental area [19]. As these cognitive functions were associated with the D1R [10–12, 18, 20–22], it can be hypothesized that these brain regions subserve the occurrence of ADHD symptoms through pathological changes in the D1R. Whereas activated microglia expressed the D1R in patients with neurodegenerative disease [39] and was attenuated by a D1R agonist in experimental animals [40, 41]. Furthermore, other model animals suggested a role of an interaction between D1R and neuroinflammation in the pathophysiology of ADHD [42, 43]. However, the potential interaction between the D1R and activated microglia in ADHD has not yet been studied.

The purposes of this present PET study employing two tracers were (1) to investigate whether the D1R and activated microglia were altered in individuals with ADHD compared with TD subjects and (2) to investigate whether both phenomena correlated with each other or with clinical severities, including cognitive impairments, in the brain regions implicated in ADHD etiology. Based on the downregulated D1-like receptors and possible involvements of neuroinflammation in ADHD [23–29], we hypothesized lower D1R and higher activated microglia in individuals with ADHD than those in TD subjects. Because the activated microglia expressed the D1R [39, 41], we hypothesized correlations between these phenomena. For an exploratory hypothesis, we also estimated possible correlations of D1R or activated microglia with ADHD clinical severities [10–12, 18, 20–22, 24, 25, 29].

Materials and methods

Participants

The individuals with ADHD were recruited from the Hamamatsu University School of Medicine Hospital. The inclusion criteria for individuals with ADHD were as follows: (1) diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) [1]; (2) being older than 18 years of age; and (3) never taking neurotropic drugs, such as methylphenidate, atomoxetine, antipsychotics, antidepressants, anxiolytics, or hypnotics. The exclusion criteria for the individuals with ADHD were as follows: (1) the presence of gross abnormalities in T2 or FLAIR head magnetic resonance images (MRI); (2) the presence of a major medical illness; (3) the regular consumption of a significant amount of alcohol, because individuals with alcohol dependence have shown decreased activated microglia [44]; (4) the habit of smoking regularly, because subjects who smoked have shown decreased activated microglia [45]; (5) full-scale IQ < 80; and (6) a history of neurological or psychiatric disorders other than ADHD. The

individuals with ADHD were interviewed using Conners' Adult ADHD Diagnostic Interview for DSM-IV and the Structured Clinical Interview for DSM-IV to assess psychiatric disorders [46–48]. Age- and sex-matched TD subjects who were free from any own and first-degree family history of neurological or psychiatric disorders, including ADHD, and who did not drink or smoke regularly were also included in this study. All TD subjects were recruited from the local community with careful considerations to match age and gender between the two study groups. This study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Hamamatsu University School of Medicine. This case-control study recruited all participants from April 5, 2011 to March 9, 2016. All participants provided written informed consent after informing all procedures of this study verbally and writing. Because of no PET study measuring the D1R or activated microglia in individuals with ADHD, we estimated the required sample size as 48 with 20% dropout based on our previous PET study ($n = 40$) measuring the activated microglia in another neurodevelopmental disorder [49]. PET analyses were performed by individuals blinded to group status. The imaging data acquired here are not publicly deposited, but are available from the corresponding author on reasonable request.

Clinical variables

All the participants underwent the following psychological and cognitive assessments: the Conner's adult ADHD rating scale (CAARS) for measuring symptom severities of ADHD [50]. The Wechsler adult intelligence scale 3rd edition (WAIS-III) for measuring intelligence and cognitive ability [51]. The WAIS-III provided a score of full-scale IQ from four subscales: verbal comprehension, working memory, perceptual organization, and processing speed. The score of full-scale IQ was used for above-mentioned inclusion criteria in this study. In addition, we assessed cognitive performance by the Cambridge neuropsychological test automated battery (CANTAB), a computerized, nonlinguistic, and culturally blind cognitive test (http://www.cambridgecognition.com/cantab/). In particular, from CANTAB, we utilized the rapid visual information processing (RVP) task for measuring sustained attention, the spatial working memory task for working memory, and stop signal task for response inhibition [52, 53]. To reduce unusual stress derived from imaging studies, which might affect motivation for completing these psychological tasks, 20 individuals with ADHD and 18 TD subjects underwent these assessments on another day within a week before or after PET and MRI measurements, and the others performed them within 2 weeks before or after the measurements.

PET data acquisition

A high-resolution brain PET scanner (SHR12000, Hamamatsu Photonics K.K., Hamamatsu, Japan) capable of yielding 47 tomographic images was employed [54]. We used [^{11}C]SCH23390 PET tracer for measuring D1R and [^{11}C](*R*)PK11195 for activated microglia [55, 56]. After backprojection and filtering (Hanning filter, cut-off frequency of 0.2 cycles per pixel), the image resolution was $2.9 \times 2.9 \times 3.4$ mm FWHM. The voxel of each reconstructed image measured $1.3 \times 1.3 \times 3.4$ mm. After the intravenous injection of each tracer (i.e., [^{11}C]SCH23390 and [^{11}C](*R*)PK11195), dynamic PET scans with 32 frames (time frames: 4×30, 20×60, and 8×300 s) were performed over 62 min in both tracers.

The binding potential (BP_{ND}) parametric images of [^{11}C]SCH23390 were estimated based on a simplified reference tissue model (SRTM), in which we used a normalized time-activity curve based on the cerebellar cortex of each participant [57]. The BP_{ND} parametric images of [^{11}C](*R*)PK11195 were also estimated based on the SRTM, in which we used a normalized mean time-activity curve based on the TD subjects as a reference tissue curve [57]. A normalized input curve was created by averaging the VOIs placed over the bilateral frontal cortex, temporal cortex, parietal cortex, occipital cortex, thalamus, basal ganglia, and cerebellar hemisphere in the TD subjects [58]. The normalized mean tissue activity curve was then used as the reference input function because a desirable reference region free from specific binding was not evident in individuals with neurodevelopmental disorders [49]. The normalized input curve derived from the TD subjects was used as the time-activity curve for the reference region of the individuals with ADHD and TD subjects. All BP_{ND} parametric images were generated using PMOD 3.2 software (PMOD Technologies, Ltd., Switzerland).

MRI data acquisition

MRI was performed to determine the regions of concern for establishing volumes of interest (VOIs) and to investigate possible brain structural abnormalities using a 1.5 T MRI scanner (Signa HDxt, GE, Orlando, Florida, USA) with the following acquisition parameters: three-dimensional mode sampling; repetition time, 25 ms; echo time, 6 ms; flip angle, 30°; number of excitations, 0.75; field of view, 24 cm; matrix size, 256×192; number of slices, 128; slice thickness, 1.5 mm; and slice direction, sagittal [anterior commissure-posterior commissure (AC-PC) line was horizontal in the sagittal image]. The MRI parameters and a mobile PET gantry allowed us to reconstruct the PET images parallel to the AC-PC line without reslicing. Thus, we were able to locate the VOIs in the target regions of the

original PET images [59]. We manually set VOIs in the ACC, DLPFC, OFC, dorsal striatum, thalamus, nucleus accumbens, ventral tegmental area, supplementary motor area, and frontal eye field. Examples of VOIs are shown in Supplementary Fig. 1. We transferred each VOI onto the corresponding BP_{ND} parametric images and obtained BP_{ND} values of each tracer for each VOI.

Statistical analyses

Statistical analyses were performed using SPSS, version 25 (IBM, Armonk, NY). Categorical variables were assessed using χ^2-test; Continuous variables were assessed using independent-sample t tests. The statistical threshold was assumed to be $P < 0.05$ (two-sided).

To compare the BP_{ND} values of each tracer in the individuals with ADHD with the TD subjects, we used analysis of variance (ANOVA) with group status (ADHD vs. TD) as a between-subjects factor and VOIs as a within-subjects factor. The statistical threshold in ANOVA was assumed to be $P < 0.05$. In the presence of significant main interactions between group status and VOIs, regional contrasts in the nine VOIs were examined using post hoc t tests with the Bonferroni correction for multiple comparisons with a statistical threshold of $P < 0.0056$ (=0.05/9 VOIs).

For secondary outcomes, to investigate correlations between BP_{ND} values of [^{11}C]SCH23390 and [^{11}C](*R*)PK11195 in the each VOI of the individuals with ADHD, we conducted Pearson's correlations analysis in the 9 VOIs with the Bonferroni correction for multiple comparisons with a statistical threshold of $P < 0.0056$ (=0.05/9 VOIs). Furthermore, group differences in the calculated correlations were examined employing Fisher's r-to-z transformation in the 9 VOIs with the Bonferroni correction for multiple comparisons with a statistical threshold of $P < 0.0056$ (=0.05/9 VOIs).

As exploratory analyses, to clarify the clinical correlates of the BP_{ND} values in each tracer in the individuals with ADHD and TD subjects, Pearson's correlation analysis was conducted between the BP_{ND} values of 9 VOIs and the 11 clinical variables in each tracer. Considering the large number of correlations examined (i.e., 99 correlations), a false discovery rate (FDR) corrected P value < 0.05 was employed as the threshold for statistical significance to avoid false negative (type II error) results [60].

Results

Twenty-four psychotropic-naïve individuals with ADHD (inattentive type, 22; hyperactive-impulsive type, 0; mixed type, 2) and 24 age- and sex-matched TD subjects participated (Table 1), while one individual with ADHD could not complete the RVP task due to fatigue. The individuals with ADHD showed significantly higher scores for all subscales of the CAARS than the TD subjects ($P < 0.001$; Table 1). Although we excluded participants with full-scale IQ < 80 as one of the exclusion criteria, the individuals with ADHD showed significantly lower scores for processing speed than the TD subjects ($P = 0.049$; Table 1). The individuals with ADHD showed significantly lower scores for the RVP task than the TD subjects ($P = 0.02$; Table 1).

Table 1 Characteristics of participants.

Characteristic	Individuals with ADHD ($n = 24$)	TD subjects ($n = 24$)	Statistics	P value
Age, mean (SD), years	32.3 (8.0)	32.1 (8.6)	$t = 0.11$	0.92
Sex, No. male/female	11/13	11/13	$\chi^2 < 0.001$	>0.99
Injected dose, mean (SD), MBq				
[^{11}C]SCH23390	299.9 (60.8)	314.4 (57.8)	$t = -0.85$	0.40
[^{11}C](*R*)PK11195	301.0 (84.0)	299.6 (54.3)	$t = 0.07$	0.95
CAARS, mean (SD)				
Inattention	25.8 (6.6)	9.5 (4.9)	$t = 9.71$	<0.001
Hyperactivity	17.0 (8.2)	10.0 (5.2)	$t = 3.52$	<0.001
Impulsivity	19.3 (8.5)	10.7 (5.7)	$t = 4.12$	<0.001
Problem with self-concept	12.7 (4.6)	5.4 (3.6)	$t = 6.09$	<0.001
WAIS-III, mean (SD)				
Full-scale IQ	99.2 (14.6)	102.5 (10.6)	$t = -0.90$	0.37
Verbal comprehension	101.1 (15.9)	99.1 (11.2)	$t = 0.50$	0.62
Working memory	93.1 (14.9)	98.8 (9.8)	$t = -1.57$	0.12
Perceptual organization	97.5 (12.8)	105.0 (13.4)	$t = -2.00$	0.05
Processing speed	99.0 (13.5)	106.0 (10.2)	$t = -2.02$	0.049
CANTAB, mean (SD)				
RVP task	0.92 (0.04)[a]	0.94 (0.04)	$t = -2.37$	0.02
Spatial working memory task	19.5 (20.6)	16.1 (17.7)	$t = 0.62$	0.54
Stop signal task	172.3 (59.2)	158.0 (54.4)	$t = 0.87$	0.39

ADHD attention-deficit/hyperactivity disorder, *TD* typically developing, *CAARS* Conner's adult ADHD rating scale, *WAIS-III* Wechsler adult intelligence scale 3rd edition, *CANTAB* Cambridge neuropsychological test automated battery, *RVP* rapid visual information processing.

[a]Missing for 1 individual with ADHD.

Injected doses of [^{11}C]SCH23390 and [^{11}C](*R*)PK11195 were not significantly different between the individuals with ADHD and TD subjects (Table 1). Representative PET images of [^{11}C]SCH23390 and [^{11}C](*R*)PK11195 are shown in Supplementary Fig. 2. In the [^{11}C]SCH23390 PET measurements, we found a significant main effect of VOIs ($F_{8,414} = 503.58$, $P < 0.001$) and a significant interaction between group status and VOIs ($F_{8,414} = 2.23$, $P = 0.03$) in ANOVA. Post hoc t tests indicated that the individuals with ADHD showed significantly lower [^{11}C]SCH23390 BP_{ND}

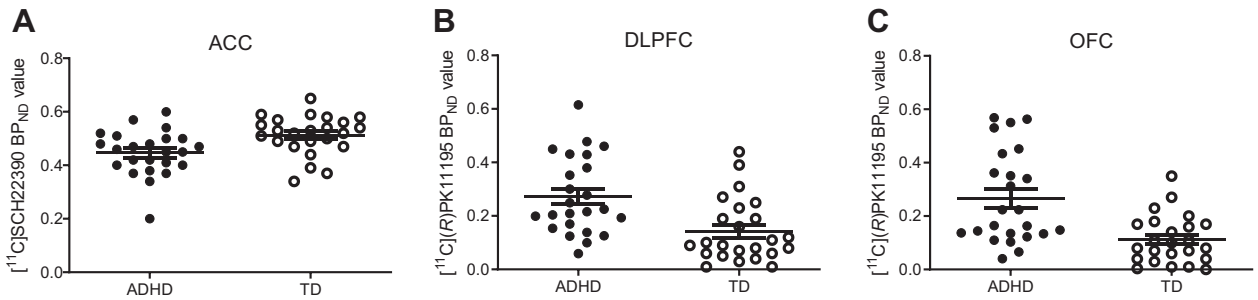

Fig. 1 Regional binding potential (BP_{ND}) values of [^{11}C]SCH23390 and [^{11}C](*R*)PK11195. a Plots represent the regional [^{11}C]SCH23390 BP_{ND} values in the anterior cingulate cortex (ACC). **b** Plots represent the regional [^{11}C](*R*)PK11195 BP_{ND} values in the dorsolateral prefrontal cortex (DLPFC). **c** Plots represent the regional [^{11}C](*R*)PK11195 BP_{ND} values in the orbitofrontal cortex (OFC). The closed circles represent the individuals with ADHD. The open circles represent the TD subjects. Error bars represent the standard errors. The differences in these BP_{ND} values between ADHD and TD subjects reached statistical significance at Bonferroni-corrected $P < 0.05$.

values in the ACC than the TD subjects ($t_{46} = -3.11$, $P = 0.003$, Bonferroni-corrected $P < 0.05$; Fig. 1a, Supplementary Fig. 3 and Supplementary Table 1). In the [^{11}C](*R*)PK11195 PET measurements, we also found a significant main effect of VOIs ($F_{8,414} = 487.48$, $P < 0.001$) and a significant interaction between group status and VOIs ($F_{8,414} = 2.01$, $P = 0.04$) in ANOVA. Post hoc *t* tests revealed that the individuals with ADHD had significantly higher [^{11}C](*R*)PK11195 BP_{ND} values in the DLPFC ($t_{46} = 3.40$; $P = 0.001$, Bonferroni-corrected $P < 0.05$) and OFC ($t_{46} = 3.86$; $P < 0.001$, Bonferroni-corrected $P < 0.05$) than the TD subjects (Fig. 1b, c, Supplementary Fig. 4 and Supplementary Table 2). Given that the lowest [^{11}C]SCH23390 BP_{ND} value in the ACC and the highest [^{11}C](*R*)PK11195 BP_{ND} value in the DLPFC among the individuals with ADHD were notably deviated than the others, we investigated the sensitivity of our model to removing these values, and the statistical significance remained (ACC, $t_{45} = -2.97$, $P = 0.005$, Bonferroni-corrected $P < 0.05$; DLPFC, $t_{45} = 3.40$; $P = 0.003$, Bonferroni-corrected $P < 0.05$).

We found significant positive correlations between BP_{ND} values of [^{11}C](*R*)PK11195 and [^{11}C]SCH23390 in the DLPFC ($r = 0.56$, $P = 0.005$, Bonferroni-corrected $P < 0.05$) and OFC ($r = 0.57$, $P = 0.004$, Bonferroni-corrected $P < 0.05$) of individuals with ADHD (Table 2, Fig. 2a, b and Supplementary Fig. 5). The correlations in both the DLPFC ($z = 2.55$, $P = 0.005$, Bonferroni-corrected $P < 0.05$) and the OFC ($z = 3.15$, $P < 0.001$, Bonferroni-corrected $P < 0.05$) were significantly different between the ADHD and TD groups as revealed by Fisher's *r*-to-*z* transformation (Table 2 and Supplementary Table 3), indicating that the correlations were significantly specific to the individuals with ADHD.

Furthermore, Fig. 3 shows the significant correlations between the BP_{ND} values of each tracer and the clinical variables of the individuals with ADHD. The [^{11}C]SCH23390 BP_{ND} values in the ACC showed a significant negative correlation with scores on the hyperactivity subscale of the CAARS in the individuals with ADHD ($r = -0.66$, $P < 0.001$, FDR-corrected $P < 0.05$; Fig. 3a). The [^{11}C](*R*)PK11195 BP_{ND} values in the DLPFC was significantly negatively correlated with scores on the processing speed ($r = -0.66$, $P < 0.001$, FDR-corrected $P < 0.05$; Fig. 3b) and RVP tasks ($r = -0.62$, $P = 0.001$, FDR-corrected $P < 0.05$; Fig. 3c). The [^{11}C](*R*)PK11195 BP_{ND} values in the OFC was also significantly negatively correlated with scores on the RVP task ($r = -0.64$, $P < 0.001$, FDR-corrected $P < 0.05$; Fig. 3d). We did not find any significant correlations between the BP_{ND} values of each tracer and the clinical variables of the TD subjects (Supplementary Fig. 6).

Table 2 Regional correlation coefficients between [^{11}C]SCH23390 binding potential (BP_{ND}) values and [^{11}C]PK11195 BP_{ND} values.

	Individuals with ADHD		TD subjects		Group difference	
Brain region	*r*	*P* value	*r*	*P* value	*z*	*P* value
DLPFC	0.56	0.005[a]	−0.16	0.46	2.55	<0.001[a]
OFC	0.57	0.004[a]	−0.31	0.14	3.15	<0.001[a]

ADHD attention-deficit/hyperactivity disorder, *TD* typically developing, *DLPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex.
[a]Bonferroni-corrected $P < 0.05$.

Discussion

To the best of our knowledge, this is the first study to examine any involvement of the D1R or activated microglia in individuals with ADHD. The present study showed lower D1R expression in the ACC and higher microglial activation in the DLPFC and OFC of individuals with ADHD than the TD subjects. The decreased anterior cingulate D1R showed significant correlations with the severe

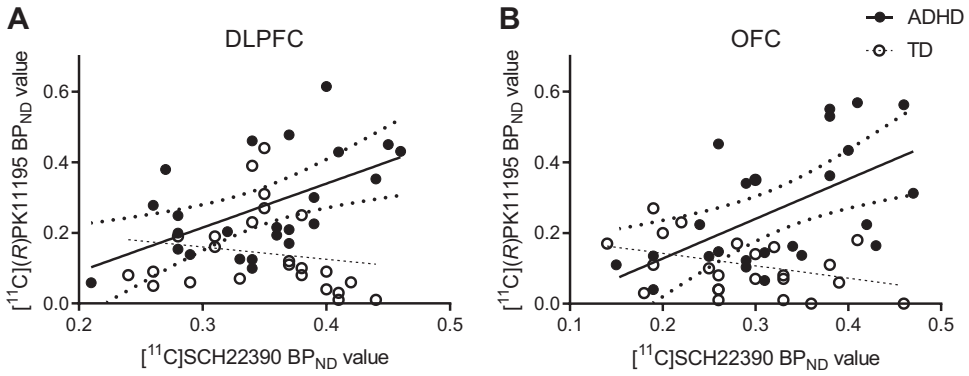

Fig. 2 Regional correlations between [^{11}C]SCH23390 binding potential (BP_{ND}) values and [^{11}C](*R*)PK11195 BP_{ND} values. Scatterplots show correlations in the dorsolateral prefrontal cortex (DLPFC) (**a**) and the orbitofrontal cortex (OFC) (**b**). The closed circles represent the individuals with ADHD. The open circles represent the TD subjects.

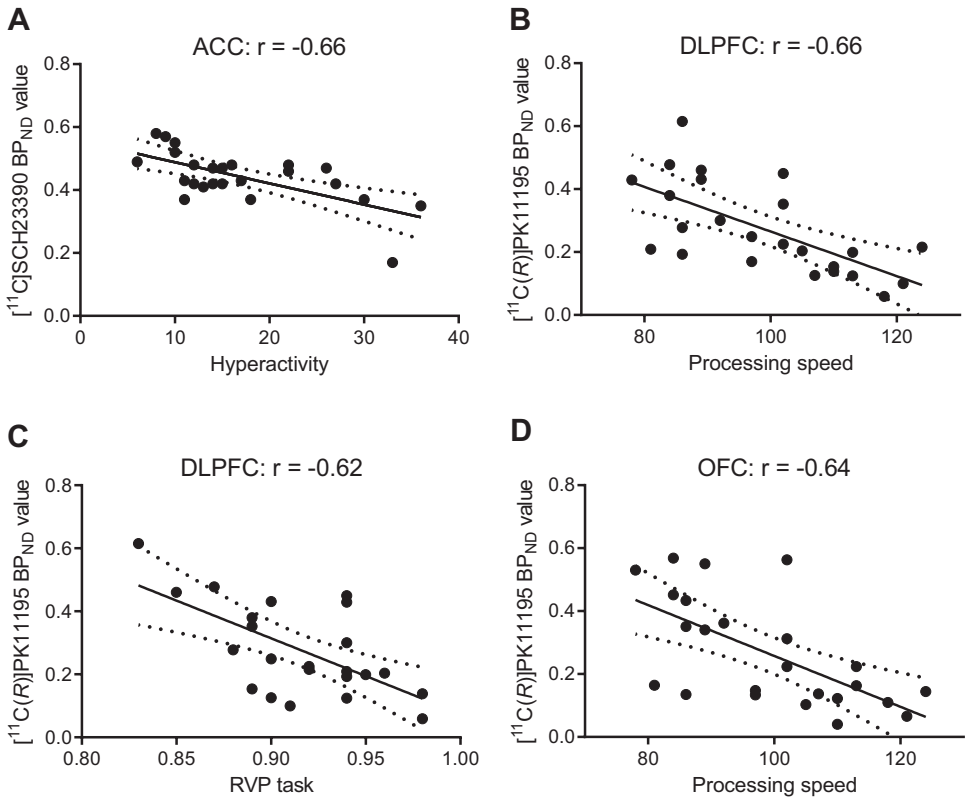

Fig. 3 Regional correlations between the binding potential (BP_{ND}) values of each PET tracer and clinical variables of the individuals with ADHD. Scatterplots show correlations between the regional [^{11}C]SCH23390 BP_{ND} values in the anterior cingulate cortex (ACC) and scores on the hyperactivity subscale of the Conner's adult ADHD rating scale (CAARS) (**a**), between the regional [^{11}C](*R*)PK11195 BP_{ND} values in the dorsolateral prefrontal cortex (DLPFC) and scores on the processing speed (**b**), between that in the DLPFC and scores on the rapid visual information processing (RVP) task (**c**), and between that in the orbitofrontal cortex (OFC) and scores on the processing speed (**d**) in the individuals with ADHD. These correlations reached statistical significance at FDR-corrected $P < 0.05$.

hyperactivity symptom of ADHD. The increased microglial activation in both the DLPFC and OFC was significantly correlated with decreased sustained attention. The increased microglial activation in the DLPFC was also significantly associated with a worse score of processing speed in individuals with ADHD. Moreover, the individuals with ADHD showed significant and aberrant correlations between the D1R and activated microglia in the DLPFC and OFC.

This study showed that decreased D1R expression in the ACC was associated with severe hyperactivity in individuals with ADHD. Previous studies supported the links between the D1R, the ACC, and the pathophysiology of ADHD by revealing decreased D1R expression in the ACC of an ADHD animal model [23], altered functional connectivity in the ACC contributing to the hyperactivity of ADHD [61, 62], and a relationship between the decreased functional connectivity and the decreased D1R expression in the ACC of TD subjects [63]. Taken together with the current results, the altered functional connectivity coexisting with the decreased D1R expression in the ACC might be involved in ADHD pathophysiology. Another line of studies has suggested a potential role of anterior cingulate D1R in the treatment for the clinical and cognitive symptoms of ADHD, as a D1R agonist was shown to increase

brain activation in an experimental animal model [64] and to improve attentional deficit in psychiatric patients in a randomized controlled trial [65]. Given the effects of neurofeedback training, especially for the ACC on ADHD symptoms such as inattention and hyperactivity, by improving the self-regulation of brain activation [66, 67], the neurofeedback training for the ACC under the condition of D1R agonist stimulation might be an efficient treatment for ADHD.

The present study showed that increased microglial activation in the DLPFC was associated with worse performance score on tasks of processing speed and attention in individuals with ADHD. Previous studies have shown that the effects of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) on the DLPFC improve the performance of processing speed and attention in TD subjects [68–71] and symptom severity and cognitive impairments in ADHD subjects [72, 73]. Indeed, our current study has shown that tDCS on the prefrontal cortex increases dopamine release in the ventral striatum [74]. Because the tDCS and TMS attenuated microglial activation in animal studies [75, 76], suppressing the activated microglia by these noninvasive neural stimulations was considered a therapeutic alternative for ADHD. Since the attenuation of microglial activation was also induced by a D1R agonist [40], the use of a D1R agonist was further supported as a promising treatment for ADHD.

Our study showed that the increased activated microglia in the OFC was associated with a worse performance of processing speed in individuals with ADHD. A worse processing speed performance has been associated with an increased microglial activation in patients with encephalitis or in individuals infected with human immunodeficiency virus [77, 78] as well as with altered brain activation of the OFC in patients with schizophrenia [79]. As a D1R agonist attenuated the activated microglia and increased brain activation [40, 41, 64], the use of a D1R agonist is expected to improve processing speed by affecting not only the activated microglia but also brain activation in the OFC of individuals with ADHD.

In addition, our study showed positive and specific correlations between the microglial activation and D1R in the DLPFC and OFC of ADHD subjects. Because the activated microglia themselves expressed the D1R and decreased along with the decreased D1R expression [39, 41], an attempt to reduce microglial activation may ameliorate the D1R-related neuronal hypoactivities. Since a D1R antagonist reduced the therapeutic effects of methylphenidate according to the decreased neuronal activities [10–12], a D1R agonist that increased neural activities might be suitable for the treatment of ADHD together with the attenuation of microglial activation.

Our study showed significant associations between some brain regions (i.e., ACC, DLPFC, and OFC) and clinical variables (i.e., hyperactivity, processing speed, and attentional ability) in the individuals with ADHD (Fig. 3). These findings were not reported in previous neuroimaging studies, most of which were conducted with functional MRI [19, 37, 38]. This may be due to the difference in methodologies used, i.e., in our study, the D1R and activated microglia were examined using PET. Our previous PET study with [^{11}C](*R*)PK11195 showed a significant increase in microglial activation in almost all brain regions in adults with autism spectrum disorder (ASD) at the same statistical threshold as the current study, while we found the significant microglial activation in two clusters in ADHD adults. Previous meta-analyses of gray matter volume abnormalities in ADHD and ASD subjects highlighted two and five clusters, respectively [80, 81]. These findings suggest that the abnormality of the brain network is more localized in ADHD than in ASD. Indeed, some cognitive impairments in ADHD are commonly seen in ASD, but the severities of the symptoms are quite different [82, 83]. Depicting these differences in neuroimaging and cognitive studies helps to explain the difference in the underlying pathophysiology among neurodevelopmental disorders such as ADHD and ASD.

Our study has some potential limitations. First, our ADHD subjects with cognitive impairments in few domains (Table 1) did not show previously reported associations between the cognitive functions and D1R [10–12, 18, 20–22]. To find associations between the D1R and various cognitive impairments in individuals with ADHD, a larger sample size might be needed to detect cognitive impairments in broad domains. Second, based on our results of significant correlations between the D1R and activated microglia (Fig. 2), we suggested that a D1R agonist might be suitable for attenuating the activated microglia in ADHD. Because our study had a cross-sectional design, it is appropriate to conduct a longitudinal study to clarify the effect of the D1R agonist on activated microglia with or without external current/magnetic stimulation. Third, although many new-generation TSPO tracers for activated microglia are reported to have an rs6971 polymorphism, the first-generation tracer [^{11}C](*R*)PK11195 is free from it [84], which allowed TSPO PET measurements to be performed without genotyping tests in the current study. Fourth, alterations in D2/D3 receptors and dopamine release were reported in previous PET studies on ADHD using [^{11}C] raclopride [85, 86], which can be used to estimate dopamine release because of its lower affinity to the D2/D3 binding site than endogenous dopamine. In contrast, since a higher binding affinity of [^{11}C]SCH23390 does not allow measurement of dopamine release, we only evaluated the availability of the D1R in the current study [87].

Conclusions

The current study demonstrated significantly decreased D1R expression in the ACC correlated with symptom severity in individuals with ADHD. In addition, the significantly increased microglial activation in the DLPFC and OFC were found to correlate with cognitive impairments. Given the significant specific and positive correlations between the D1R and activated microglia in the DLPFC and OFC of ADHD individuals, the use of a D1R agonist might be suitable as a novel therapy by attenuating microglial activation in individuals with ADHD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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