

Fig. 1. Worksheet used in the tracing and copying tasks.

and Tsujii (2011) except for the number of shapes. We selected seven simple shapes from the nine shapes in the original task because schoolteachers requested for shortening the administration time. These shapes were outlined with dotted lines, and the students traced these shapes. In the copying task, the students looked at models of the shapes (which were identical to those used in the tracing task) and copied them. The α factors were .71 and .65 in tracing and copying tasks, respectively, which indicated that these tasks had acceptable levels of internal consistencies. In addition, tracing and copying tasks were positively correlated with the Japanese standardized achievement test (Tatsuno et al., 2009), which meant that these tasks had the convergent validity ($r = .27$ and $.28$ in tracing and copying tasks, respectively).

2.2.1.2. Handwriting fluency tasks. Berninger, Mizokawa, and Bragg (1991) developed a simple task for measuring handwriting fluency that involves writing as many letters of the alphabet as possible in order within one minute. Berninger et al. (1997) found a high inter-rater reliability for this task ($r = .97$). In addition, this task has been used and cited in many handwriting studies (see Berninger, 1999, for a review), and the psychometric information from this task is available as a developed test that is linked to other writing skills. We applied this task to the Japanese language and developed a handwriting fluency task for Hiragana and Katakana. In this task, the children wrote as many Hiragana or Katakana characters as possible in their Japanese syllabary order within one minute. These tasks were positively correlated with the Japanese standardized achievement test (Tatsuno et al., 2009), which indicated the convergent validity ($r = .13$ and $.32$ in Hiragana handwriting and Katakana handwriting, respectively).

2.2.1.3. Spelling tasks. We revised the spelling tasks in Fujita and Tsujii (2011) to develop shorter version that were more convenient for the teachers. We selected 24 Hiragana characters and created nine concrete words composed of these characters (Table 1). Illustrations of the nine selected words were presented to the students in an A4-size worksheet. The Hiragana spelling task required the students to look at an illustration and write its name in Hiragana. The Katakana spelling

Table 1
Materials used in each spelling task.

Hiragana	Katakana	Kanji	
い ゆ う (dragon)	リ ュ ウ (dragon)	赤 (red)	足 (foot)
たぬき (raccoon dog)	タヌキ (raccoon dog)	町 (town)	耳 (ear)
ろけっと (rocket)	ロケット (rocket)	青 (blue)	音 (sound)
くぎ (nail)	クギ (nail)	雨 (rain)	草 (grass)
ふで (writing brush)	フデ (writing brush)	天気 (weather)	右 (right)
だちょう (ostrich)	ダチョウ (ostrich)	左 (left)	
おやゆび (thumb)	オヤユビ (thumb)	糸 (string)	
へそ (navel)	ヘソ (navel)	夕立 (shower)	
ほん (book)	ホン (book)	空 (sky)	

Note. Words in parentheses indicate the English words corresponding to each Japanese word.

task was identical to the Hiragana spelling task, except that students were required to write the name of the illustration in Katakana (Table 1). The Kanji spelling task included 14 words composed from 16 Kanji characters. The students were required to look a Hiragana word and then write the Kanji characters corresponding to that word.

The α factors of Hiragana, Katakana, and Kanji spelling were .88, .94, and .78, respectively, which indicated that these tasks had sufficient levels of internal consistencies. In addition, these three spelling tasks were positively correlated with the Japanese standardized achievement test (Tatsuno et al., 2009), which meant that these tasks had the convergent validity ($r = .40, .45$, and $.53$ in Hiragana, Katakana, and Kanji spelling tasks, respectively).

2.2.2. Questionnaire

2.2.2.1. Japanese version of home form of the ADHD-RS. The ADHD-Rating Scale-IV (ADHD-RS; DuPaul, Power, Anastopoulos, & Reid, 1998) was developed to measure the two major characteristics of ADHD: Inattentive (9 items) and Hyperactive-impulsive (9 items). Previous research has confirmed sufficient reliability and validity for the home form of the ADHD-RS (DuPaul, Power, McGoey, Ikeda, & Anastopoulos, 1998; DuPaul et al., 1998). Tani, Okada, Ohnishi, Nakajima, and Tsujii (2010) developed the Japanese version of the ADHD-RS home form and showed that it had good reliability and validity. The parents/guardians of the children rated each item on a 4-point Likert scale ranging from “Not at all or rarely (0)” to “Sometimes (1),” “Often (2),” or “Very often (3).” Therefore, the higher a child’s score on the ADHD-RS, the more ADHD symptoms the child displayed.

2.2.2.2. Japanese version of the DCDQ. The developmental coordination disorder questionnaire (DCDQ) is a parent questionnaire designed to screen for pediatric DCD (Wilson et al., 2009; Wilson, Kaplan, Crawford, Campbell, & Dewey, 2000). Nakai, Yoshizawa, Kawatani, and Wilson (2009) recently developed a Japanese version of the DCDQ (DCDQ-J), and Nakai et al. (2011) have reported on a relatively large-scale school-based study describing the applicability of the DCDQ-J to a community-based population of Japanese children. The DCDQ-J is a 15-item parent rating scale that includes three factors: Control during movement (6 items), Fine motor (4 items), and General coordination (5 items). Each item is scored on a 5-point scale as follows: “Not at all like your child (1),” “A bit like your child (2),” “Moderately like your child (3),” “Quite a bit like your child (4),” and “Extremely like your child (5),” with higher scores indicating better motor coordination.

2.3. Procedures

2.3.1. Writing task

Classroom teachers handed the worksheets to their students in the classroom. Teachers explained the procedures to students and timed the administration time. All procedures were conducted in a group instruction format.

Experienced speech therapists and a psychologist scored the students’ performances on all the tasks. We trained each scorer using the coding sheet prior to this study. Scorers coded each character in writing tasks as correct, incorrect, and blank. We counted the blank as incorrect. The coding sheet illustrated the definition of each code and concrete examples. We calculated the percent of correct characters in tracing, copying, and spelling tasks. We counted the number of correct characters in handwriting fluency task.

2.3.2. Questionnaire

We sent each questionnaire to the parents/guardians of students via the classroom teachers. The parents/guardians who agreed to participate in this study answered the questionnaire and sent it back. The responses from the 816 respondents were analyzed.

2.4. Statistical analysis

We used the PASW Statistics 18.0 software package (SPSS Inc.) for the statistical analysis. We first calculated the descriptive statistics (mean and standard deviations) for the tracing, copying, handwriting, and spelling tasks. In addition,

Table 2
Descriptive statistics of writing performances and each score in ADHD-RS and DCDQ-J.

	Boys			Girls			<i>t</i>
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	
Writing task							
Tracing	405	78.84	22.89	468	88.03	16.11	6.77***
Copying	405	72.84	22.48	468	83.52	20.13	7.35***
Hiragana handwriting fluency	395	18.50	7.17	459	17.84	7.25	–1.33
Katakana hand writing fluency	385	19.34	7.37	448	20.77	7.72	2.74**
Hiragana spelling	405	88.95	15.64	468	91.81	12.42	2.96**
Katakana spelling	405	77.09	25.89	468	84.11	21.76	4.30***
Kanji spelling	405	84.41	16.35	468	86.27	14.22	1.78
ADHD-RS							
Inattentive	375	6.07	4.92	452	4.51	3.85	–4.97***
Hyperactive-impulsive	382	3.79	4.06	450	2.29	2.86	–5.97***
Total score	372	9.83	8.36	444	6.79	6.17	–5.76***
DCDQ-J							
Control during movement	379	21.28	5.09	448	20.25	4.70	–2.96**
Fine motor	387	13.89	3.46	455	15.61	3.23	7.40***
General coordination	384	16.17	4.00	453	17.12	3.96	3.39***
Total score	377	51.26	10.95	442	53.00	10.15	2.35*

* $p < .05$.

** $p < .01$.

*** $p < .001$.

we computed the descriptive statistics (mean and standard deviations) for each ADHD-RS and DCDQ-J subscale score. Because some previous studies in Japan demonstrated the gender difference in writing performance (e.g., Kono, Hirabayashi, & Nakamura, 2008; Uno et al., 2006), we used *t*-test to examine the difference between boys and girls in each writing performances and each score of ADHD-RS and DCDQ-J. A principal component analysis with a promax rotation was then performed using the seven writing performance scores. Three writing composites scores (Spelling Accuracy, Tracing and Copying Accuracy, and Handwriting Fluency) were derived from the results of the principal component analysis. Third, we calculated the Pearson Product Moment Correlations between the ADHD-RS and DCDQ-J subscale scores and the three writing composites scores. Finally, a multiple regression analysis with backward elimination was performed to predict each composite writing score using the children's sex and their ADHD-RS and DCDQ-J subscale scores. The number of data inputs in the analysis varied because missing data were excluded.

3. Results

3.1. Descriptive statistics

Table 2 shows the descriptive statistics for writing performances and for each ADHD-RS and DCDQ-J subscale scores by sex. The girls demonstrated significantly higher writing performance scores than the boys in all the tasks except for the Kanji spelling and Hiragana handwriting fluency. By contrast, two ADHD-RS subscale and total scores were significantly higher in the boys than in the girls. Although the boys had significantly higher DCDQ-J Control during movement score than the girls, the girls had significantly higher Fine motor, General coordination, and total scores than the boys.

3.2. Principal component analysis

Seven writing performance scores were submitted to a principal component analysis with a promax rotation. Using Kaiser's criterion and the scree plot (2.54, 1.52, 1.01, .56, .051, etc.), we derived three interpretable components from the component structure. Table 3 shows the component loadings for principal component analysis with promax rotation of writing performances and the inter-component correlations. Based on the magnitude of each component loading, we named Component 1 "Spelling Accuracy", component 2 "Tracing and Copying Accuracy", and component 3 "Handwriting Fluency". Spelling Accuracy was moderately correlated with the other two components. The correlations between Tracing and Copying Accuracy and Handwriting Fluency were not significant. Using the results of the principal component analysis, we created three composite scores. We calculated the *z*-score of each writing performance score and then summed them by component.

3.3. Correlation analysis

Table 4 shows the correlations between the composite writing performance scores and the ADHD-RS and DCDQ-J scores. Tracing and Copying Accuracy was moderately correlated with Fine motor on the DCDQ-J and weakly correlated with the other ADHD-RS and DCDQ-J scores. No significant correlations were found between Handwriting Fluency and the other scores. Spelling Accuracy was moderately correlated with Inattentive on the ADHD-RS and Fine motor on the DCDQ-J; it was weakly correlated with other subscale scores and with the ADHD-RS and DCDQ-J total scores.

Table 3
Component loadings for principal component analysis with promax rotation of writing performances and inter-component correlations.

Writing performance	Component loadings		
	C1	C2	C3
Hiragana spelling	.93	–.12	–.13
Katakana spelling	.83	–.06	.07
Kanji spelling	.58	.28	.12
Tracing	.01	.86	–.17
Copying	–.08	.88	.10
Hiragana handwriting fluency	–.11	–.14	.91
Katakana handwriting fluency	.12	.11	.81
Inter-component loadings			
	C1	C2	C3
C2	.35***	–	
C3	.29***	.07*	–

Note. Component loadings > .50 are in bold face.

* $p < .05$.

*** $p < .001$.

Table 4
Correlations between writing performances and each score in ADHD-RS and DCDQ-J.

	ADHD-RS			DCDQ-J			
	Inattentive	Hyperactive-impulsive	Total score	Control during movement	Fine motor	General coordination	Total score
Spelling accuracy	–.289*** (n = 768)	–.185*** (n = 773)	–.255*** (n = 758)	.078* (n = 768)	.253*** (n = 782)	.125*** (n = 777)	.165*** (n = 760)
Tracing and copying accuracy	–.178*** (n = 768)	–.130*** (n = 773)	–.158*** (n = 758)	.095** (n = 768)	.319*** (n = 782)	.191*** (n = 777)	.221*** (n = 760)
Handwriting fluency	–.065 (n = 768)	.018 (n = 773)	–.031 (n = 758)	.053 (n = 768)	.058 (n = 782)	.010 (n = 777)	.056 (n = 760)

Note.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 5
Multiple regression analysis with backward elimination predicting composite writing performance scores from sex, and ADHD and DCD symptoms.

	Spelling Accuracy		Tracing and Copying Accuracy		Handwriting Fluency	
	$R^2 = .102$		$R^2 = .131$		$R^2 = .015$	
	β	p	β	p	β	p
Sex (Girls)			.188	<.001		
ADHD-RS						
Inattentive	–.220	<.001			–.182	.001
Hyperactive-impulsive					.153	.005
DCDQ-J						
Control during movement						
Fine motor	.157	<.001	.267	<.001		
General coordination						

3.4. Multiple regression analysis

Table 5 shows the results of the multiple regression analysis with backward elimination for predicting the composite writing performance scores using ADHD and DCD symptoms and sex. In the correlation analysis, we found that the subscale scores of both the ADHD-RS and DCDQ-J correlated more strongly with writing performance than did the total scores. Therefore, we used each subscale score as an independent variable for predicting writing performances in the multiple regression analysis.

Inattentive was negatively associated with Spelling Accuracy and Handwriting Fluency. Hyperactive-impulsive was also significantly associated with Handwriting Fluency. By contrast, Fine motor on the DCDQ-J was positively associated with Spelling Accuracy and with Tracing and Copying Accuracy. Sex (female) was positively associated with Tracing and Copying Accuracy.

4. Discussion

The purpose of the present study was to examine the relationships between ADHD and DCD symptoms and writing performance in Japanese second grade students from regular classrooms. We hypothesized that ADHD and DCD symptoms were related to writing performance in Japanese children. The Japanese language has three character systems and it differs from English in many aspects. Therefore, this study uniquely contributed to understanding the relationships between developmental characteristics and writing performance for this specific type of language (Japanese).

The descriptive statistics showed that the girls demonstrated higher writing performance scores than the boys in all of the tasks except for the Kanji spelling and Hiragana handwriting fluency. In addition, gender differences were also found in each ADHD-RS and DCDQ-J subscale scores and total scores. Previous studies about writing performance (e.g., Graham, Berninger, Weintraub, & Schafer, 1998; Kono et al., 2008; Uno et al., 2006) reported the same results. The result of this study is consistent with these previous findings. The gender differences in ADHD-RS and DCDQ-J are also consistent with previous Japanese studies (Nakai et al., 2011; Tani et al., 2010).

Using principal component analysis, we derived three interpretable components from the seven writing performance scores and created composite scores for each component: Spelling Accuracy, Tracing and Copying Accuracy, and Handwriting Fluency. Three composite writing scores significantly correlated each other. However, the Pearson correlation coefficient between Tracing and Copying Accuracy and Handwriting Fluency was very low. Although these two components involve graphomotor aspects of writing, these components represent somewhat different aspects: accuracy and fluency. Students who trace or copy accurately are not necessarily able to write words fluently. This difference may lead to the low correlation between these two components.

We assessed the developmental characteristics of the children using the ADHD-RS and DCDQ-J, and we examined the correlations between three composite writing scores and each developmental characteristic. Spelling Accuracy and Tracing and Copying Accuracy were significantly correlated with all scores in ADHD-RS and DCDQ-J. Especially, we found relatively high correlation between Spelling Accuracy and Inattentive, and Fine motor, and between Tracing and Copying Accuracy and Fine motor. On the other hand, Handwriting fluency did not correlate with any scores in ADHD-RS and DCDQ-J. Because these correlation analyses did not control for each variable, we then conducted the multiple regression analysis. The multiple regression analysis revealed that the developmental characteristics had differing correlation patterns with the composite writing performance scores. Sex significantly predicted only Tracing and Copying Accuracy. A high Inattentive score predicted poor Spelling Accuracy and Handwriting Fluency. This result is consistent with previous findings that have addressed the relationship between the attention component and writing (e.g., Amundson & Weil, 2001; Tsai et al., 2011). The relationship between the inattention component and spelling suggests that children with attention problems have difficulty associating phonemes with graphemes. Moreover, the children with attention problems could not maintain their attention on the handwriting fluency task, which required them to continue to respond over one minute. Hyperactive-impulsive predicted Handwriting Fluency. The children with more Hyperactive-impulsive symptoms had more fluent handwriting skills. This result differs from those of Resta and Eliot (1994), who found no writing differences between ADHD children with and without hyperactive behavior. This discrepancy may be due to the different methods for measuring writing. We used performance in the handwriting fluency task as our measure, and Resta and Eliot (1994) measured writing performance by the parent's subjective rating of their child's handwriting. In addition, the differing study populations (typically developing children / children with ADHD) may have affected this inconsistency.

Of the DCDQ-J subscale scores, only Fine motor predicted Spelling Accuracy and Tracing and Copying Accuracy. The other two subscale scores did not predict any writing performance scores. Previous studies (Berninger & Rutberg, 1992; Flapper et al., 2006) have reported similar relationships between fine motor skills and writing performance. Because children are required to integrate visual, motor, and conceptual abilities in the process of writing (Mercer & Mercer, 2005), children with fine motor dysfunction tend to have difficulties in writing.

5. Limitation and perspectives

In this study, we examined only handwriting and spelling skills. Writing has many other components such as content and spatial arrangement. Further researches are needed to examine the relationship between developmental characteristics and other writing components. We used a cross-sectional survey consisting only of second grade children. Therefore, we need to assess the relationships between writing performance and ADHD and DCD symptoms in a large longitudinal study to investigate causal relationships. In this study, we used only parent-rating questionnaires to assess the children's ADHD and DCD characteristics. Further research with more sensitive neuropsychological tests is needed to clarify the mechanisms by which these developmental characteristics lead to writing difficulties.

6. Conclusion

The results of this study of Japanese-speaking students are consistent with previous findings for English-speaking children. Although this study had some limitations, it provides empirical evidence that developmental characteristics such as inattention and fine motor skill are related to writing difficulties. Identifying the precise relationships between developmental characteristics and writing difficulties is an important prerequisite for developing effective interventions.

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小中学生の不注意および多動・衝動的行動傾向と 攻撃性、抑うつとの関連

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Relationship among inattentive and hyperactive-impulsive behavior, aggression, and depression in Japanese elementary and junior high school students

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The present study examines the relationship among inattentive, and hyperactive-impulsive behavior, aggression, and depression in elementary school and junior high school students. The participants were 3,885 children and their teachers and caregivers. Children's inattentive and hyperactive-impulsive behavior was rated by their teachers and caregivers (ADHD-RS). Children rated aggression (HAQ-C) and depression (DSRS-C) themselves. Inattentive and hyperactive-impulsive behavior rated by teachers and caregivers were positively related to aggression and depression. Inattention predicted higher levels of aggression and depression. Inattentive and hyperactive-impulsive behavior as rated by teachers was more highly related to depression than those behaviors as rated by caregivers. The relationships among inattentive, and hyperactive-impulsive behavior, aggression, and depression were almost the same for both elementary school and junior high school students. This study suggests the importance of assessing inattentive and hyperactive-impulsive behavior from multiple views to examine the relationship between inattentive and hyperactive-impulsive behavior and mental health problems.

Key words: inattention, hyperactivity-impulsivity, aggression, depression.

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近年、教育や発達臨床場面において、著しい不注意や多動を特徴とする注意欠陥多動性障害 (Attention-Deficit/Hyperactivity Disorder: ADHD) の子どもたちに対する支援に多くの関心が寄せられている。ADHD は、不注意や多動性・衝動性という行動特徴から、教師や親からの叱責を受けやすい (齊藤・青木, 2010)。その結果、自尊心の低下や気分の落ち込み、攻撃的反抗などの二次障害が生じやすく (齊藤・青木, 2010)、それらの二次障害を防ぐことを視野に入れた支援が必要になる。一方で、学校現場には医学的診断を受けて

いないが、不注意や多動・衝動的な行動傾向を示す子どもが在籍しており、それらの子どもたちの適応や精神的健康について検討することも重要である。本研究では、通常学級に在籍している小中学生の不注意や多動・衝動的な行動傾向と抑うつ、攻撃性との関連性を検討した。

ADHD に認められる二次障害は、大きく分けて外在化障害と内在化障害の二種類に分けることができる (齊藤・青木, 2010)。外在化障害とは、親や教師からの叱責、仲間からの拒絶などによって生じる孤独感や怒りの感情を、攻撃や反抗として自己の外の対象に向けて表現するものである。先行研究では、ADHD と攻撃性との関連が指摘されており、例えば Connor, Chartier, Preen, & Kaplan (2010) は、ADHD の診断を受けている子ども 268 名と診断を受けていない統制群

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の子ども 100 名の攻撃性を比較したところ、測定した全ての攻撃性尺度（表出性攻撃・能動的攻撃・反応的攻撃）において ADHD の子ども達の得点が高いことを報告している。King, Waschbusch, Pelham, Frankland, Corkum, & Jacques (2009) では、ADHD 群、メチルフェニデートを服薬している ADHD 群、統制群の 3 群を対象に、コンピューターゲームを用いた攻撃行動の測定を行っている。その結果、服薬なしの ADHD 群は対戦相手からかわれた条件においては統制群よりも能動的攻撃および反応的攻撃をした人数が多かったことが示されている。

ADHD に認められる二次障害のもう一つが内在化障害である。内在化障害とは、仲間からの拒絶などによる葛藤やそれに基づく感情を、気分の落ち込みや不安などの内的体験として表現するものである。ADHD の子どもは、不注意や多動という行動特徴ゆえに、叱責されたり他者から拒絶されることが多くなり、その結果として抑うつなどの否定的な感情を経験しやすくなる（田中・中山, 2007）。Chronis-Tuscano, Molina, Pelham, Applegate, Dahlke, Overmyer, & Lahey (2010) は、4 歳から 6 歳の間に ADHD の診断を受けた子ども 125 名（ADHD 群）と ADHD の診断を受けていない 123 名（統制群）を対象としたコホート研究を行い、18 歳の時にうつ病の診断基準を満たしていた割合を比較した。結果、うつ病の診断基準を満たしていた人数は ADHD 群が統制群の約 4 倍であったことを報告している。

以上のように、臨床群としての ADHD 児が、高い攻撃性や抑うつを示すことを考えれば、一般の子どもにおいても不注意や多動性・衝動的行動傾向と攻撃性や抑うつといった精神的健康上の問題との間に関連がみられるかもしれない。現在、ADHD はカテゴリー化できる障害ではなく（Levy, Hay, McStephen, Wood, & Waldman, 1997）、誰でも不注意や多動・衝動的行動傾向を示すことがあるという考え方が支持されつつあり、臨床群としての ADHD 児とそうでない子ども達の違いは、前者には神経生物学的要因によって ADHD によく見られる行動特徴が高い割合で現れるということに過ぎないと言われている（DuPaul & Stoner, 2003）。このことを考慮すると、医学的な診断を受けていなくても、不注意および多動・衝動的行動傾向の高い子ども達は、その行動特徴のために臨床群としての ADHD 児と同様の精神的健康上の問題を抱えている可能性が考えられる。

本研究では ADHD の診断を受けている子どもたちに認められる、不注意および多動・衝動的行動傾向と攻撃性および抑うつとの関連が、通常学級に在籍する小中学生にも同様にみられるのかを検討することを目的とした。その際、教師評定と保護者評定の二つの視点から行動傾向を包括的に把握し、それぞれの評定

値と本人評定による攻撃性、抑うつとの関連を検討した。

方 法

調査協力者と手続き

A 県 X 市にある全ての公立小学校（8 校）、中学校（4 校）の通常学級に在籍している児童・生徒（計 6,675 名）およびその担任教師と保護者に調査協力を求めた。X 市は、約 80,000 の人口を有する中規模都市である。その立地から、同市の居住者は、近隣の市の大企業に勤務する者や地元の中小企業や工場に勤める者など、様々な世帯状況の者が混在しており、日本の人口統計学的状態を適切に代表していると考えられる。なお、協力校の教員との協議の結果、小学 1 年生は自己評定が困難であると考え、調査を実施しなかった。調査者が各協力校を訪問し、担当教諭に調査内容の説明と依頼を行った。児童・生徒およびその保護者に対しては、担任教諭を通じて調査の依頼と調査用紙の配布を行った。教師評定については、クラス担任が行った。保護者評定については、約 94% が母親であり、約 5% が父親、その他が祖父母であった。調査は、教師評定が 8 月、本人評定および保護者評定が 9 月に実施された。本研究では、本人評定、教師評定、保護者評定が揃い、かつ欠損値のみられなかった 3,885 名を分析対象とした。対象者の内訳を Table 1 に示す。なお、本研究では、特別支援学級に所属する児童・生徒には調査を実施しなかった。

質問紙

不注意および多動・衝動的行動傾向 不注意および多動・衝動的行動傾向を測定するために、Dupaul, Power, Anastopoulos, & Reid (1998) が開発した ADHD Rating Scale-IV (ADHD-RS) を用いた。この尺度は、ADHD の主な特徴である“不注意（9 項目）”と“多動性・衝動性（9 項目）”の 2 下位尺度から構成されている。ADHD-RS には、教師評定版と保護者評定版があるが、いずれも同じ項目から構成されており、教師は、“新学期の初頭から現在までにおける子どもの行動を最もよく表している番号を○で囲んでください”という指示、保護者は、“過去 6 ヶ月間の子どもさんのご家庭での行動を最もよく表している番号を一つ選んで○をおつけください”という指示のもと、子どもの特徴を記述した各項目に対して、“ない、もしくはほとんどない（0 点）”“ときどきある（1 点）”“しばしばある（2 点）”“非常にしばしばある（3 点）”の 4 件法で回答する。得点が高いほど不注意および多動・衝動的行動傾向が強いことを示す。本研究では、各子どもの担任教師および保護者が ADHD-RS に回答した。ADHD-RS の日本語版の妥当性と信頼性について

Table 1
Grade and sex of participants in this survey

	Male	Female	Total
Second grade	232	255	487
Third grade	266	288	554
Fourth grade	213	240	453
Fifth grade	256	288	544
Sixth grade	242	245	487
Seventh grade	250	235	485
Eighth grade	206	242	448
Ninth grade	194	233	427
Total	1859	2027	3885

は、先行研究で確認されている (Ohnishi, Okada, Tani, Nakajima, & Tsujii, 2010; Tani, Okada, Ohnishi, Nakajima, & Tsujii, 2010)。本研究では、各評定者の因子ごとに項目の合計得点を下位尺度得点として算出した。

攻撃性 本研究では、攻撃性を感情面の怒り(短気)、認知面の敵意、行動面としての攻撃という3側面を総称するものとして捉え(山崎, 2002), Hostility-Aggression Questionnaire for Children (HAQ-C: 坂井・山崎・曾我・大芦・島井・大竹, 2000)を用いて攻撃性を測定した。HAQ-Cは、攻撃性を多面的に測定する Buss-Perry Aggression Questionnaire (BAQ: Buss & Perry, 1992)を子ども用に改変した尺度であり、BAQと同じく“敵意(6項目)”“短気(5項目)”“身体的攻撃(6項目)”“言語的攻撃(5項目)”と無関項目5項目の計27項目から構成されている。本研究では、無関項目を除く22項目を使用した。HAQ-Cには児童・生徒本人が回答した。児童・生徒は、“次の文章は、あなたにどれくらいあてはまりますか”という指示のもと、普段の自分の特徴について、“まったくあてはまらない(1点)”“あまりあてはまらない(2点)”“よくあてはまる(3点)”“とてもよくあてはまる(4点)”の4件法で回答する。尺度の妥当性と信頼性については、先行研究で確認されている(坂井他, 2000)。本研究では、因子ごとに項目の合計得点を下位尺度得点として算出した。

抑うつ 抑うつという用語には、抑うつ気分、抑うつ症状、精神疾患としてのうつ病の三つの意味が含まれるが(Compas, Ey, & Grant, 1993), 本研究では抑うつ症状に焦点をあて、Birleson Depression Self-Rating Scale for Children (DSRS-C: Birleson, 1981)の日本語版(村田・清水・森・大島, 1996)を用いて子どもの抑うつ症状を測定した。この尺度は、“楽しみの減退(6項目)”“悲哀感(6項目)”“無気力(3項目)”“活動性減退と身体症状(3項目)”の4下位尺度から構成されている。しかし、以降の研究では、2因子構造が示されており(佐藤・新井, 2002; 谷・吉橋・神谷・宮地・野村・伊藤・辻井, 2010), “活動性および楽しみの減退(10項目)”と“抑うつ気分(8項目)”の2

下位尺度として使用されることが多い(谷他, 2010)。DSRS-Cには児童・生徒本人が回答した。児童・生徒は、“わたしたちは、楽しい日ばかりではなく、ちょっとさみしい日も、楽しくない日もあります。みなさんが、この1週間どんな気持ちだったか、当てはまるところに○を書き入れてください”という指示のもと、過去1週間の気分状態について、“そんなことはない(0点)”“ときどきそうだ(1点)”“いつもそうだ(2点)”の3件法で回答する。尺度の妥当性と信頼性については、先行研究で確認されている(村田他, 1996; 谷他, 2010)。本研究では、因子ごとに項目の合計得点を下位尺度得点として算出した。

倫理的配慮

調査は浜松医科大学の倫理委員会の承認を得て行った。個人情報の保護について、X市のセキュリティポリシーを遵守することで十分な倫理的配慮のもとに実施された。調査への協力は任意であり、個人のプライバシーが保護されることを伝えた。また、研究協力校に対しては、著者が各校に出向き、学校ごとに結果のフィードバックを行った。

分析方法

教師と保護者による子どもの不注意および多動・衝動的行動傾向の評定と、子どもの自己評定による抑うつと攻撃性との関連を検討するために、下位尺度得点を用いて構造方程式モデリングによるパス解析を行った。パス解析は、攻撃性と抑うつのそれぞれについて別個のモデルを構成した。また、不注意および多動・衝動的行動傾向から攻撃性と抑うつに対する説明力について、学校段階差を検討するために小学生と中学生の二つの母集団を想定する多母集団同時分析を行った。最初に等値制約を置かないモデル(モデル1)を検討し、次に母集団間で有意な差がなかったパスと共分散に等値制約を置くモデル(モデル2)を検討し、最後にすべてのパスと共分散に等値制約を置くモデル(モデル3)を検討した。モデル間の比較は、 χ^2 値とAIC, CFIによって行った。

結 果

変数間の関連

各尺度の記述統計量をTable 2に、ADHD-RSとDSRS-C, HAQ-Cとの相関係数をTable 3に示す。ADHD-RSの評定者間の相関について、不注意は $r = .34$, 多動性・衝動性は $r = .30$ であった。ADHD-RSの下位尺度は、DSRS-CおよびHAQ-Cのほぼすべての下位尺度と有意な相関を示し、それらの値は $r = .05$ から $r = .20$ の弱い値であった。また、DSRS-CとHAQ-Cとの間にも、全ての下位尺度間で有意な相

Table 2
Descriptive statistics of study variables

	Mean	SD	α
ADHD-RS			
Teacher ratings			
Inattentive	1.35	3.39	.90
Hyperactive-Impulsive	0.64	2.23	.86
Caregiver ratings			
Inattentive	4.60	4.68	.90
Hyperactive-Impulsive	2.08	3.27	.86
HAQ-C			
Hostility	12.27	4.00	.81
Anger	10.41	3.41	.80
Physical aggression	13.34	4.32	.83
Verbal aggression	12.95	2.87	.67
DSRS-C			
Decline of activity and enjoyment	5.91	3.56	.79
Depressive mood	3.48	2.75	.75

関がみられたが、DSRS-Cの下位尺度である活動性および楽しみの減退と抑うつ気分は、言語的攻撃とは負の相関 ($r = -.34$ および $r = -.10$) を示し、それ以外の3下位尺度とは正の相関 ($r = .20$ から $r = .57$) を示した。

不注意および多動・衝動的行動傾向と攻撃性、抑うつとの関連性の検討

攻撃性に関するモデル 最初に対象者全体で分析を行った。教師評定および保護者評定によるADHD-RSの計4下位尺度から、HAQ-Cの4下位尺度に対するパスを設定し、ADHD-RSの4下位尺度間とHAQ-Cの下位尺度の誤差間に共分散を仮定する飽和モデルを設定した。結果をTable 4に示す。教師評定の不注意から敵意 ($\beta = .08, p < .001$)、短気 ($\beta = .05, p < .05$) に対して有意な正のパスがみられ、言語的攻撃 ($\beta = -.09, p < .001$) に対して有意な負のパスがみられた。教師評定の多動性・衝動性から短気 ($\beta = .08, p < .001$)、身体的攻撃 ($\beta = .11, p < .001$)、言語的攻撃 ($\beta = .11, p < .001$) に対して有意な正のパスがみられた。保護者評定の不注意から敵意 ($\beta = .12, p < .001$)、短気 ($\beta = .05, p < .05$)、身体的攻撃 ($\beta = .09, p < .001$) に対して有意な正のパスがみられ、言語的攻撃 ($\beta = -.13, p < .001$) に対して有意な負のパスがみられた。保護者評定の多動性・衝動性から短気 ($\beta = .13, p < .001$) と言語的攻撃 ($\beta = .14, p < .001$) に対して有意な正のパスがみられた。

次に、学校段階ごとの多母集団同時分析を行った。モデル1の適合度は、AIC = 144.00, CFI = 1.00であった。このモデルは飽和モデルであるため、 χ^2 値は算出されない。モデル2の適合度は、 $\chi^2(19) = 23.75$ (ns), AIC = 129.75, CFI = 1.00であった。モデル3の適合度は、 $\chi^2(28) = 349.03$ ($p < .001$), AIC = 437.03,

CFI = 0.97であった。モデル2とモデル3との差は有意であった ($\Delta\chi^2(9) = 325.28, p < .001$)。以上の結果から、モデル2を採用した。学校段階ごとのパス係数をTable 4に示す。教師評定の多動性・衝動性から短気に対するパスは、小学生では有意であったが ($\beta = .09, p < .001$)、中学生では有意ではなかった ($\beta = -.01, ns$)。

抑うつに関するモデル 最初に対象者全体で分析を行った。教師評定および保護者評定によるADHD-RSの計4下位尺度から、DSRS-Cの2下位尺度に対するパスを設定し、ADHD-RSの4下位尺度間とDSRS-Cの下位尺度の誤差間に共分散を仮定する飽和モデルを設定した。結果をTable 4に示す。教師評定の不注意から活動性および楽しみの減退 ($\beta = .12, p < .001$)、抑うつ気分 ($\beta = .09, p < .001$) に対して有意な正のパスがみられた。また、保護者評定の不注意から活動性および楽しみの減退 ($\beta = .19, p < .001$)、抑うつ気分 ($\beta = .17, p < .001$) に対して有意な正のパスがみられ、保護者評定の多動性・衝動性から活動性および楽しみの減退 ($\beta = -.12, p < .001$) に対して有意な負のパスがみられた。

次に、学校段階ごとの多母集団同時分析を行った。モデル1の適合度は、AIC = 84.00, CFI = 1.00であった。このモデルは飽和モデルであるため、 χ^2 値は算出されない。モデル2の適合度は、 $\chi^2(6) = 4.41$ (ns), AIC = 76.41, CFI = 1.00であった。モデル3の適合度は、 $\chi^2(15) = 1073.22$ ($p < .001$), AIC = 358.33, CFI = 0.96であった。モデル2とモデル3との差は有意であった ($\Delta\chi^2(9) = 1068.81, p < .001$)。以上の結果から、モデル2を採用した。学校段階ごとのパス係数をTable 4に示す。教師評定の多動性・衝動性から活動性および楽しみの減退に対するパスは、中学生では有意であったが ($\beta = -.11, p < .001$)、小学生では有意ではなかった ($\beta = .01, ns$)。

考 察

本研究では、教師評定と保護者評定による不注意および多動・衝動的行動傾向と攻撃性、抑うつとの関連について検討した。教師評定による不注意および多動・衝動的行動傾向と保護者評定による不注意および多動・衝動的行動傾向との関連は、海外 (Power, Doherty, Panichelli-Mindel, Karustis, Eiraldi, Anastopoulos, & DuPaul, 1998) および日本 (岡田・大西・谷・中島・辻井, 2011) における先行研究と同様に $r = .3$ 程度であった。教師および保護者が子どもの行動傾向を評定する場合には、観察している環境が異なっていることが予想され (学校の教室、家庭内など)、それによって評定が一致しない部分が出てきたことが予想される。ADHDに認められる不注意および多動・衝動的行動傾向を評価する場合には、複数の場面における行

Table 3
Pearson correlations among ADHD-RS, HAQ-C, and DSRS-C

	HAQ-C				DSRS-C	
	Hostility	Anger	Physical aggression	Verbal aggression	Decline of activity and enjoyment	Depressive mood
Teacher ratings						
Inattentive	.12***	.16***	.15***	-.01	.13***	.12***
Hyperactive-Impulsive	.08***	.16***	.16***	.06***	.06***	.07***
Caregiver ratings						
Inattentive	.16***	.18***	.16***	.03	.13***	.17***
Hyperactive-Impulsive	.13***	.20***	.16***	.05**	.05**	.12***

** $p < .01$, *** $p < .001$

Table 4
The results of path analyses

	HAQ-C				DSRS-C	
	Hostility	Anger	Physical aggression	Verbal aggression	Decline of activity and enjoyment	Depressive mood
Teacher ratings						
Inattentive	.08***	.09/-.01	.03	-.09	.12***	.09***
Hyperactive-Impulsive	-.01	.08	.11***	.11***	.01/-.11***	-.02***
Caregiver ratings						
Inattentive	.12***	.05*	.09***	-.13***	.19***	.17***
Hyperactive-Impulsive	.02	.13***	.05	.14***	-.12***	-.02
Explained variance	.02	.06/.03	.06	.03	.04/.03	.03

Note. Path coefficients were estimated on the basis of the total sample. When the differences between elementary and junior high schools are significant, the path coefficients are shown for elementary/junior high school.

* $p < .05$, ** $p < .01$, *** $p < .001$

動傾向を考慮することが重要であると指摘されており (Anastopoulos & Shelton, 2001; Barkley, 1998), 本研究のように両者の観点を併用することが必要である。

不注意および多動・衝動的行動傾向と攻撃性との関連

攻撃性に関しては, 全般的にパス係数の値は小さかったものの, 教師評定と保護者評定による不注意および多動・衝動的行動傾向が有意な関連を示した部分があった。敵意と短気は, 攻撃性の認知面と感情面を表す側面であり, 不表出性攻撃としてまとめられることがある (坂井他, 2000)。短気に関しては, 教師評定と保護者評定の不注意と多動性・衝動性が弱いながらも有意な関連を示した。教師や保護者の目からみて, 不注意および多動・衝動的行動傾向を強く示す子どもほど, 攻撃的な認知をしており, 怒り感情を抱いている傾向にあると考えられる。ただし, 敵意に対しては教師評定と保護者評定の多動性・衝動性が有意な関連を示さなかった。敵意は攻撃性の認知的側面であるため, 相手の行動の動機や意図などを自分なりに解釈するという情報処理過程が背景にあると考えられる。多動性・衝動性の高さは, このような行動の背景にある動機や意図の推測には結びつかないため, 関連を示さ

なかったものと考えられる。不表出性攻撃に対して, 身体的攻撃と言語的攻撃は外に攻撃性をあらわす表出性攻撃とされる (坂井他, 2000)。身体的攻撃に対しては, 教師評定による多動性・衝動性が正の関連を示し, 言語的攻撃に対しては, 教師評定と保護者評定による多動性・衝動性が正の関連を示した。一方, 保護者評定の不注意は身体的攻撃とは正の関連を示すものの, 教師評定と保護者評定の不注意は言語的攻撃と負の関連を示した。この結果は, 多動・衝動的行動傾向の高い子どもは, 実際に乱暴なことをしたり, 暴言を言ったりすることが多いが, 不注意を強く示す子どもは, 他者に対して言語的な攻撃を行わない傾向にあることを示唆している。

攻撃性に対する説明力は, 教師評定と保護者評定とあまり違いはみられなかったが, 評定者によって有意な関連を示す攻撃性の側面が異なる部分もあり, 両者の視点から不注意および多動・衝動的行動傾向を捉えることが必要である。

不注意および多動・衝動的行動傾向と抑うつとの関連

抑うつに関しては, いずれも弱い値ではあるものの, 教師評定と保護者評定の不注意が活動性および楽しみ

の減退と抑うつ気分の高さと関連した。教師あるいは保護者の目からみて不注意な子どもほど、活動性および楽しみの減退がみられやすく、抑うつ気分を経験しやすいと考えられる。一方で、保護者評定の多動性・衝動性は、活動性および楽しみの減退と負の関連を示した。また、教師評定の多動性・衝動性についても、中学生で活動性および楽しみの減退と関連がみられた。保護者や教師の目からみて多動で落ち着きのない子どもほど、活動性および楽しみの減退がみられにくい傾向があると考えられる。不注意および多動・衝動的行動傾向を示す一般の児童・生徒の抑うつなど精神的健康上の問題を考えるうえでは、不注意と多動性・衝動性という二つの側面から捉えることが必要である。

また、評定者による違いに関しては、全般的に教師評定による不注意および多動・衝動的行動傾向よりも保護者評定による不注意および多動・衝動的行動傾向の方が、抑うつに対する説明力がやや高かったが、必ずしも大きな差がみられたわけではなかった。

本研究からの示唆

本研究では、教師評定と保護者評定による不注意および多動・衝動的行動傾向が、子どもの攻撃性と抑うつに対して有意な関連を示していた。Connor et al. (2010) や Chronis-Tuscano et al. (2010) などの先行研究において、ADHD の診断を受けている子どもに認められる、不注意および多動・衝動的行動傾向と攻撃性および抑うつとの関連性が、通常学級に在籍する小中学生にも確認されたことになる。このことにより、ADHD の診断がない子どもでも不注意および多動・衝動的行動傾向が高い子ども達は精神的健康上のリスクを抱えており、支援の対象となる可能性があることを示した点は重要である。さらに本研究では、教師評定と保護者評定という二者の視点から不注意および多動・衝動的行動傾向を包括的に捉え、それぞれの視点による攻撃性と抑うつとの予測を検討し、評定者によって攻撃性および抑うつとの関連の仕方が異なる部分があることを明らかにした。評定者によって関連の仕方が異なるという点は、これまであまり検討されてきておらず、不注意および多動・衝動的行動傾向が強い子どもを理解する上で新たな視点を提供しているといえよう。

今後の課題

今後の課題としては、次の二点が挙げられる。一つ目は、縦断的な関連性を検討することである。本研究では、横断的なデータを用いて、教師と保護者評定による不注意および多動・衝動的行動傾向と子どもの自己報告による抑うつや攻撃性との関連を検討した。本研究の結果をより強く支持するためには、ある時点で

教師や保護者からみた不注意および多動・衝動的行動傾向と1年後や数年後の不適応状態（攻撃性、抑うつなど）との関連を検討することが必要である。

二つ目は、教師評定と保護者評定で不注意および多動・衝動的行動傾向と攻撃性、抑うつとの関連性に違いが生じるメカニズムを明らかにすることである。本研究では、教師評定と保護者評定とで関連する側面や関連の程度に若干の違いがみられた。教師評定による ADHD-RS も保護者評定による ADHD-RS も、高い妥当性と信頼性を備えた尺度である (DuPaul et al., 1998)。教師評定と保護者評定の違いが生じる理由としては、実際に子どもが学校と家庭で異なる行動特徴を示している可能性と、教師と保護者が同じ行動について異なる基準で評定している可能性の二つが考えられる。学校においては、多動や不注意をそれほど示すことなく過ごしている子どもでも、家庭に戻ると多動や不注意を示しやすくなるのかもしれない。あるいは、教師は学級集団のなかで相対的に子どもを捉えている一方で、保護者は自分の子どものみをみているために、評定にずれが生じている可能性も考えられる。教師評定と保護者評定の違いがどのように生じているのか、そしてそれらの違いが攻撃性や抑うつとの関連性にどのように影響しているのかについて、より詳細に検討していくことが必要である。

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Microglial Activation in Young Adults With Autism Spectrum Disorder

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Context: A growing body of evidence suggests that aberrant immunologic systems underlie the pathophysiologic characteristics of autism spectrum disorder (ASD). However, to our knowledge, no information is available on the patterns of distribution of microglial activation in the brain in ASD.

Objectives: To identify brain regions associated with excessively activated microglia in the whole brain, and to examine similarities in the pattern of distribution of activated microglia in subjects with ASD and control subjects.

Design: Case-control study using positron emission tomography and a radiotracer for microglia— $[^{11}\text{C}](\text{R})$ -(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3 isquinoline carboxamide) ($[^{11}\text{C}](\text{R})$ -PK11195).

Setting: Subjects recruited from the community.

Participants: Twenty men with ASD (age range, 18-31 years; mean [SD] IQ, 95.9 [16.7]) and 20 age- and IQ-matched healthy men as controls. Diagnosis of ASD was made in accordance with the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised.

Main Outcome Measures: Regional brain $[^{11}\text{C}](\text{R})$ -PK11195 binding potential as a representative measure of microglial activation.

Results: The $[^{11}\text{C}](\text{R})$ -PK11195 binding potential values were significantly higher in multiple brain regions in young adults with ASD compared with those of controls ($P < .05$, corrected). Brain regions with increased binding potentials included the cerebellum, midbrain, pons, fusiform gyri, and the anterior cingulate and orbitofrontal cortices. The most prominent increase was observed in the cerebellum. The pattern of distribution of $[^{11}\text{C}](\text{R})$ -PK11195 binding potential values in these brain regions of ASD and control subjects was similar, whereas the magnitude of the $[^{11}\text{C}](\text{R})$ -PK11195 binding potential in the ASD group was greater than that of controls in all regions.

Conclusions: Our results indicate excessive microglial activation in multiple brain regions in young adult subjects with ASD. The similar distribution pattern of regional microglial activity in the ASD and control groups may indicate augmented but not altered microglial activation in the brain in the subjects with ASD.

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AUTISM SPECTRUM DISORDER (ASD) is a group of neurodevelopmental disorders characterized by pervasive abnormalities in social interaction and communication and by repetitive and restricted behavioral patterns and interests. Autism spectrum disorders include autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified.¹ Recent population-based surveys^{2,3} showing that ASD is more common than previously believed have aroused serious public concern worldwide. Although the neurobiologic basis for ASD remains poorly understood, a growing body of

research^{4,5} suggests that immune abnormalities are a contributing factor to the development of ASD. Several genetic studies link ASD with genes that are associated with various immune functions,

*For editorial comment
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including the HLA antigen⁶ and the major histocompatibility complex class III molecule, such as complement C4B.^{7,8} Systemic abnormalities of the immune system have been one of the most common and long-standing reported findings in subjects with ASD.^{9,10} Notably, increased production of cytokines (eg,

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Table 1. Demographic Characteristics of the Subjects*

Variable	Mean (SD) [Range]	
	Control (n = 20)	ASD (n = 20)
Age, y ^b	22.6 (5.3) [17.8-35.5]	23.3 (4.0) [18.6-31.9]
WAIS-III full IQ ^c	102.8 (12.5) [81.0-131.0]	95.9 (16.7) [81.0-140.0]
ADI-R		
Social	NA	20.6 (5.1) [10.0-29.0]
Communication	NA	15.2 (4.4) [8.0-24.0]
Stereotype	NA	4.3 (2.2) [3.0-10.0]
ADOS		
Social	NA	6.4 (3.0) [4.0-11.0]
Communication	NA	6.2 (2.7) [2.0-13.0]
Stereotype	NA	1.0 (0.9) [0-3.0]
Faux Pas Test	NA	21.2 (8.6) [3.0-34.0]
Y-BOCS	NA	11.0 (6.4) [0-28.0]
DCDQ-J total	NA	60.4 (12.0) [42.0-73.0]

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; DCDQ-J, Japanese version of the Developmental Coordination Disorder Questionnaire; NA, not applicable; WAIS-III, Wechsler Adult Intelligence Scale, third edition; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

*All subjects were men.

^bP = .63.

^cP = .15.

interleukin 6 [IL-6], tumor necrosis factor, and macrophage chemoattractant protein-1) has been observed in peripheral samples and the brains of ASD subjects.¹¹⁻¹⁶ In general, plasma cytokine levels in ASD subjects are widely distributed and show substantial overlap with control subjects, implying that there is a subset of ASD subjects with high levels of such cytokines. In addition, several studies¹⁷⁻²⁰ have identified specific antibodies against human brain epitopes in the serum of mothers of children with ASD, as well as in children with ASD, although autoantibodies are found in only 10% to 15% of the children with ASD. These findings argue in favor of the participation of the immune system in the pathogenesis of a subset of ASD subjects.

Microglia are resident brain cells that sense pathologic tissue alterations.^{21,22} The first microglial precursors colonize the brain during the embryonic and fetal phases of development.^{23,24} They develop into brain macrophages and perform immune functions. Upon exposure of the brain to any form of insult, such as infection, trauma, or ischemia, the microglia are rapidly activated. When activated, microglia produce neurotoxic substances, including proinflammatory cytokines (ie, tumor necrosis factor and IL-1 β) and oxygen species (ie, hydrogen peroxide and superoxide). However, under certain conditions, activated microglia can produce anti-inflammatory cytokines such as IL-10 and transforming growth factor- β , which have neuroprotective effects in experimental animal models of traumatic injury and stroke.^{25,26} Furthermore, experimental studies^{27,28} have demonstrated that microglia play a role in the maintenance of synaptic integrity in the uninjured brain.

Recently, Vargas and colleagues¹⁶ determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles in brain tissues from the cerebellum, midfrontal, and cingulate gyrus obtained at au-

topsy from children and adults with ASD. Immunocytochemical examination revealed marked activation of microglia and astroglia. Microglial responses were diffusely distributed in the cortex and subcortical areas, as well as the cerebellum, and were present as microglial nodules or as part of a prominent accumulation of perivascular macrophages. More recently, Morgan and colleagues²⁹ quantitatively assessed activated microglia in the dorsolateral prefrontal cortex of postmortem brains from children and adults with ASD. They found that the microglia were markedly or marginally activated in most cases examined. Transcriptomic analysis of the autistic brain by Voineagu and colleagues³⁰ has shown the presence of 2 modules in the ASD brain: a neuronal module enriched for known autism susceptibility genes, including neuronal-specific factors, such as ataxin 2-binding protein 1, and a module enriched for immune genes and glial markers. The latter immune-glial module has a less pronounced genetic component and thus is most likely either a secondary phenomenon or the result of environmental factors. Despite the striking features of microglial activation in the pathogenesis of ASD, to our knowledge, there is no information on the patterns and characteristics of the distribution of microglial activation in the whole brain in ASD subjects.

To address this issue, we conducted a positron emission tomography (PET) analysis using the radiocarbon (¹¹C)-labeled (R)-(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide) (¹¹C](R)-PK11195), a radiotracer that specifically binds to activated microglia.³¹⁻³³ This procedure permitted us to visualize the activated microglia in vivo in the whole brain. In this study, we initially determined the distribution of [¹¹C](R)-PK11195 binding potential (BP) in the whole brain of young adults with ASD and then identified several brain regions associated with the activation of microglia. Subsequently, we compared the levels of [¹¹C](R)-PK11195 BP in the identified brain regions. Because microglia may be prenatal in origin,^{23,24} and because ASD is typically diagnosed by 3 years of age, we hypothesized that the regional variability of the [¹¹C](R)-PK11195 BP in the identified brain regions is similar between ASD and control subjects, whereas the magnitude of [¹¹C](R)-PK11195BP in ASD subjects is greater than that of controls in all the regions. To test this hypothesis, we carefully recruited subjects with no history of epilepsy or medication because epileptic seizures and psychotropic drugs can influence the condition of microglial activation.³⁴⁻³⁷

METHODS

SUBJECTS

The ethics committees of the Hamamatsu University School of Medicine approved this study. Written informed consent was obtained from all subjects and their guardians after they had been provided a detailed explanation of the study procedures. Twenty men with ASD and 20 age- and IQ-matched typically developing male subjects participated in this study (**Table 1**). All subjects were right-handed and had an IQ of greater than 80. None of the subjects were tobacco smokers, and none were

taking any medication, including psychotropic drugs. All of them were physically healthy. At the time of scanning, all the subjects had no symptoms of inflammation and were not under stressful conditions. All the subjects with ASD were diagnosed by 2 trained child psychiatrists (K.N. and T.S.) according to the *DSM-IV-TR*.¹ The ASD diagnosis was confirmed for all cases using the Autism Diagnostic Interview-Revised (ADI-R)³⁸ and the Autism Diagnostic Observation Schedule (ADOS)³⁹ module-4 by trained clinicians (K.J.T. and K.M., respectively). As a result, 15 of 20 ASD subjects were diagnosed as having autistic disorder and the remaining 5 were considered to have pervasive developmental disorder not otherwise specified on the basis of the ADOS scores, although all 20 subjects met the ADI-R criteria for autistic disorder. None of the ASD subjects was classified as having regressive autism, the classification of which was based on clinical characteristics using both parental reporting and answers to questions on the ADI-R regarding language loss (question 11) and social skills (question 25). The ASD subjects did not have any other psychiatric comorbidity disorders, as confirmed by the Structured Clinical Interview for *DSM-IV* Axis I disorders.⁴⁰ In addition, they had no notable dysmorphism, neurocutaneous abnormalities, significant neurologic deficits, history of epileptic seizures, or disorders known to be associated with autism, such as fragile X syndrome, neurofibromatosis, or tuberous sclerosis. Fragile X syndrome was excluded by determining the CGG repeat number in the *FMR1* gene. We measured the markers of inflammation in the blood in the ASD subjects, including the serum C-reactive protein and white blood cell count. Both levels in all the ASD subjects were within normal range. None of the ASD subjects had any history of inflammatory or allergic diseases, except 2 subjects who had had atopic dermatitis in their childhood. One of the ASD subjects had a family history of major depression (his mother). In the remaining 19 subjects, there was no family history of any chronic inflammatory diseases or neuropsychiatric conditions. In the ASD subjects, the social cognitive disability and the degree of repetitive and/or obsessive behavior and interests were evaluated by the Faux Pas Test⁴¹ and Yale-Brown Obsessive Compulsive Scale,^{42,43} respectively. Current motor coordination problems were assessed by the Japanese version of the Developmental Coordination Disorder Questionnaire.⁴⁴ All control subjects were found to be mentally and physically healthy on the basis of comprehensive assessments of their medical histories and neuropsychiatric examinations.

MAGNETIC RESONANCE IMAGING AND PET PROCEDURES

As described previously,^{33,45} we obtained 3-dimensional magnetic resonance images (MRIs) just before PET measurements using a 0.3-T MRI unit (MRP7000AD; Hitachi Medical) and a high-resolution brain PET scanner having an intrinsic resolution of $2.9 \times 2.9 \times 3.4$ mm at full-width at half maximum and a 163-mm axial field of view, and yielding 47 PET images simultaneously (SHR 12000; Hamamatsu Photonics), respectively. All MRI and PET scans were set parallel to the anterior-posterior intercommissural line.⁴⁵ Before dynamic PET scanning, a 20-minute transmission scan was performed for attenuation correction using a ⁶⁸Ge/⁶⁸Ga source. Then, after a bolus intravenous injection of a 350-MBq dose of [¹¹C](R)-PK11195, we performed 32 serial PET scans (time frames: 4×30 second, 20×60 second, and 8×300 second) for 62 minutes. In quantitative PET brain imaging, the motion artifact is the important degrading factor. Therefore, we fixed the head of each subject by using a thermoplastic face mask, observed subjects carefully during each scan, and confirmed that all the subjects had remained immobilized.

IMAGE ANALYSIS AND KINETIC MODELING

The brain, particularly in cortical subregions, is known to be sensitive to a partial volume effect that sometimes occurs during the measurement of small brain structures and that leads to an underestimation of tracer activity. In this study, we used the following previously described procedure to minimize the contribution of the partial volume effect.^{33,45} First, we adjusted the MRI voxel size to the PET voxel size 3-dimensionally using image-processing software (DrView; Asahi Kasei) on a Sun workstation (HyperSPARC ss-20; Sun Microsystems). Then, these reformatted MRIs with 3-dimensional scales and coordinates identical to those of the PET images were used as anatomic landmarks for the regions of interest (ROIs) setting. Subsequently, by referring to areas on the MRIs as anatomical landmarks, the ROIs were carefully drawn to avoid the involvement of either the sulci or ventricles. An investigator masked to the subject's condition placed 3 ROIs over the bilateral cerebellar cortices, midbrain, and bilateral thalami on the MRIs. These ROIs were then transferred onto the corresponding dynamic [¹¹C](R)-PK11195 images.

To assess activated microglial density in the brain, we analyzed the [¹¹C](R)-PK11195 time-activity curves (TACs) on the basis of a simplified reference tissue model^{46,47} because the regional brain [¹¹C](R)-PK11195 BP (a ratio of binding and dissociation rate constants, k_3/k_4) estimated by the simplified reference tissue model is reported to correlate with the magnitude of microglial activity.^{33,48} Because the decrease of TACs was sharpest in the cerebellar ROI among the 3 ROIs examined in the control group, we assumed that the specific binding would be the least in this region. A normalized input curve was first created by averaging the TACs from the ROIs placed over the bilateral cerebellar cortices in the control group. Then, the normalized mean input curve was used as the reference input function of the simplified reference tissue model in the ASD and control subjects because a desirable reference region free from specific binding was not evident in the ASD subjects.

Using biomedical imaging software (PMOD, version 3.0; PMOD Technologies), we constructed whole-brain parametric maps of the [¹¹C](R)-PK11195 BP for the subsequent voxel-based analysis using Statistical Parametric Mapping software (SPM5; <http://www.fil.ion.ucl.ac.uk/spm>). The [¹¹C](R)-PK11195 BP maps were normalized to the Montreal Neurological Institute space, as defined by the MRI T1 template implemented in SPM5. The extracerebral structures were then masked by demarcating cerebral regions on spatially normalized MRIs. Finally, the normalized and masked BP maps were smoothed with an 8-mm full-width at half maximum gaussian filter.

In addition to the voxel-based analysis, which is suitable for an exploratory examination of altered tracer distribution in the brain, we performed a volume of interest (VOI)-based analysis because it enabled us to generate quantitative differences in [¹¹C](R)-PK11195 BP in specific regions. For this purpose, we placed additional spherical VOIs of 5-mm radius, which centered on the peak voxel derived from the results of the voxel-based analysis, on [¹¹C](R)-PK11195 BP maps for each of the subjects. The VOIs selected were the bilateral cerebellum, brainstem, splenium of the corpus callosum, bilateral fusiform gyri, bilateral superior temporal gyri, and the bilateral anterior cingulate, bilateral orbitofrontal, left midfrontal, and right parietal cortices. Averaged [¹¹C](R)-PK11195 BP values for each VOI were obtained in the ASD and control groups.

VOXEL-BASED MORPHOMETRY

To investigate possible differences in brain structure between the ASD and control groups, we conducted voxel-based morphometry. For this purpose, we used a 3-T MRI scanner (Signa Excite;

General Electric Medical Systems) to obtain T1-weighted volumetric images scanned by the inversion recovery-prepared fast spoiled gradient recalled acquisition protocol as follows: repetition time = 11.0 milliseconds, echo time = 5.0 milliseconds, preparation time = 450 milliseconds, flip angle 20°, number of excitations = 1, field of view = 24.0 cm, matrix = 256 × 256, auto-zero-fill interpolation = 512, location per slab = 160, slice thickness = 1.2 mm, and voxel size = 0.94 × 0.94 × 1.2 mm. The T1-weighted volumetric images were analyzed using the VBM5.1 toolbox (<http://www.fil.ion.ucl.ac.uk/spm/ext/>) implemented in SPM5 with the default parameters. Estimates of the absolute gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes were obtained after the automatic brain segmentation procedure had been carried out by VBM5.1. The total intracranial volume was calculated as the sum of the volumes of the GM, WM, and CSF.

STATISTICAL ANALYSIS

The demographic and clinical variables of the ASD and control groups were compared by the unpaired *t* test using statistical software (PASW Statistics version 18; SPSS Japan Inc). The level of statistical significance was set at *P* < .05.

The voxel-based analyses of the [¹¹C](R)-PK11195 BP maps were conducted using SPM5. For the SPM5 analysis of the [¹¹C](R)-PK11195 BP maps, between-group comparisons were performed to explore regional differences in the [¹¹C](R)-PK11195 BP using the *t* test for each voxel without a proportional scaling of the [¹¹C](R)-PK11195 BP maps. We also performed exploratory correlation analyses between the regional changes in [¹¹C](R)-PK11195 BP values and the severity of clinical features in ASD subjects using SPM5. The scores on the ADOS, ADI-R, Faux Pas Test, Yale-Brown Obsessive Compulsive Scale, and the Japanese version of the Developmental Coordination Disorder Questionnaire were variables of interest. To test hypotheses about the region-specific effects of these variables, the estimates were compared using 2 linear contrasts (positive or negative correlation). In the SPM5 analyses, values of *P* < .05 were statistically significant after adjustment for the false discovery rate in the whole-brain multiple comparisons.

In the VOI-based analyses, we tested the main effect of the diagnosis of ASD on [¹¹C](R)-PK11195 BP values derived from 13 brain regions using 2-way analysis of variance, in which statistical significance was set at *P* < .05. For comparisons of clinical variables between subgroups of ASD subjects, a Mann-Whitney test was performed.

To assess the differences in segmented brain volumes between groups in the voxel-based morphometry analysis, we conducted a multivariate analysis of covariance using PASW software with group (ASD and control) as a between-subject factor, segmented brain regional absolute volume (GM, WM, and CSF) as a within-subject factor, and intracranial volume as a covariate. The statistical significance level was set at *P* < .05. Second, for the GM analysis, the normalized, modulated, and smoothed GM image segments in each group were entered into a voxel-wise 2-sample *t* test analysis in SPM5. An absolute threshold mask of 0.30 was used to avoid possible edge effects around the border between GM and WM. The statistical threshold was set at *P* < .05 after the false discovery rate correction. Data were presented as mean (SD).

RESULTS

Characteristics of all the subjects are summarized in Table 1. There was no significant difference in age or IQ between the 2 groups.

COMPARISON OF [¹¹C](R)-PK11195 BP BETWEEN ASD SUBJECTS AND CONTROLS

The tissue TACs of [¹¹C](R)-PK11195 are shown in **Figure 1A**. After the administration of [¹¹C](R)-PK11195, the radioactivity in 3 ROIs over the cerebellum, midbrain, and thalamus of a representative control subject decreased with time. The TACs in an ASD subject decreased less sharply than those in the control subject, indicating a time-course accumulation of [¹¹C](R)-PK11195 in the respective brain structures. **Figure 1B** shows MRI-PET fusion parametric images of [¹¹C](R)-PK11195 BP in the representative control and ASD subjects. A marked increase in [¹¹C](R)-PK11195 binding was observed across widespread areas of the brain of the representative ASD subject.

In the voxel-based analysis, we found greater [¹¹C](R)-PK11195 BP in multiple brain regions in the ASD group than in the control group; the brain regions with increased [¹¹C](R)-PK11195 BP included the cerebellum, brainstem (midbrain and pons), subcortical region (corpus callosum), limbic region (anterior cingulate cortex), and the frontal, temporal, and parietal regions (**Table 2** and **Figure 2**). Among the brain regions, the left cerebellum showed the most prominent *z* score. There were no voxels in which controls had a significantly higher [¹¹C](R)-PK11195 BP compared with that of the ASD group. In the ASD group, there was no significant difference in [¹¹C](R)-PK11195 BP between the 2 diagnoses—that is, autistic disorder (*n* = 15) or pervasive developmental disorder not otherwise specified (*n* = 5).

On the basis of the results of the voxel-based analysis, we then conducted VOI-based analysis. We placed 14 spherical VOIs of 5-mm radius, which centered on the peak voxels listed in Table 2. In accordance with the findings derived from the voxel-based analysis, the [¹¹C](R)-PK11195 BP was significantly higher in ASD subjects than in control subjects throughout all VOIs (**Figure 3**; *F*_(13,532) = 17.62, *P* < .001). As shown in Figure 3, the mean [¹¹C](R)-PK11195 BP was highest in the brainstem, followed by the left cerebellum, right orbitofrontal cortex, right anterior cingulate cortex, and other regions in the control group. The corresponding rank order was essentially the same in the ASD group. Thus, the pattern of distribution of [¹¹C](R)-PK11195 BP values throughout the VOI was quite similar between the 2 groups. **Figure 4** shows a scatterplot of [¹¹C](R)-PK11195 BP from the 4 VOIs (the left cerebellum, midbrain, right orbitofrontal cortex, and right anterior cingulate cortex) in the ASD and control groups. Although the overall average level of [¹¹C](R)-PK11195 BP was higher in the ASD group than in the control group, the BPs of some ASD subjects overlapped those of the controls in the 4 VOIs.

CORRELATION BETWEEN [¹¹C](R)-PK11195 BP AND SYMPTOMS IN ASD

Relationships between the regional changes in [¹¹C](R)-PK11195 BP values and the clinical features of ASD subjects were evaluated by voxel-based exploratory correlation analyses using SPM5. There was no voxel for which significant correlations were observed between [¹¹C](R)-

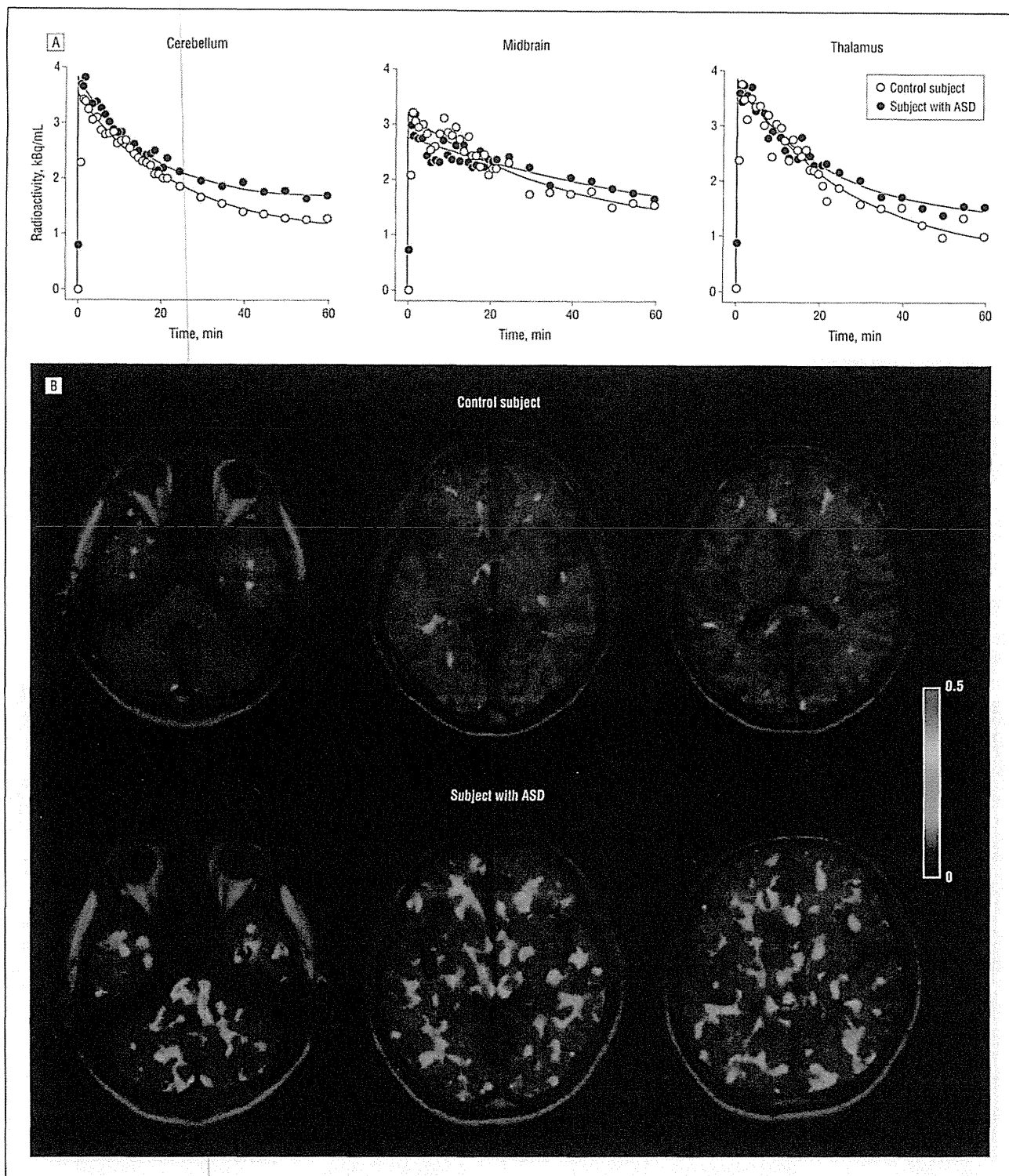


Figure 1. Results of positron emission tomography image analyses in a healthy control subject and a subject with autism. A, Scattergrams showing the time-activity curves of radiocarbon (^{11}C)-labeled (*R*)-(1-[2-chlorophenyl]-*N*-methyl-*N*-[1-methylpropyl]-3 isoquinoline carboxamide) ($[^{11}\text{C}](R)$ -PK11195) for regions of interest in the cerebellum, midbrain, and thalamus in a subject with autism spectrum disorder (ASD) and a control subject. B, Magnetic resonance imaging–positron emission tomography fusion parametric images of $[^{11}\text{C}](R)$ -PK11195 binding potential in a subject with ASD and a control subject. The left brain is shown on the right. The color bar indicates a level of binding potential.

PK11195 BP and the scores on the Faux Pas Test, Yale-Brown Obsessive Compulsive Scale, ADI-R, ADOS, or the Japanese version of the Developmental Coordination Disorder Questionnaire after the correction of whole-brain multiple comparisons (data not shown).

In the VOI-based analysis, we also conducted correlation analyses between $[^{11}\text{C}](R)$ -PK11195 BP in each VOI and clinical variables, and we found no significant correlations. We divided the ASD group into 2 subgroups, a High-BP and Not-High-BP group, on the basis of the

Table 2. Results of the Whole-Brain Voxel-Based Statistical Parametric Mapping Analyses of [¹¹C](R)-PK11195 Binding Potential: Increase in Binding in the Subjects With ASD^a

Brain Regions	Coordinates			Voxel Level	
	x	y	z	Corrected <i>P</i> Value	<i>z</i> Score
Cerebellum					
Left lobuli 7, 8, and 9	-10	-58	-38	.03	4.82
Right lobuli 7 and 8	32	-76	-48	.04	3.77
Brainstem (midbrain and pons)	10	-38	-42	.03	4.56
Frontal region					
Left middle frontal gyrus, BA10, BA46	-44	50	12	.03	3.89
Left orbitofrontal cortex, BA11	-8	48	-4	.03	3.93
Right orbitofrontal cortex, BA47	14	30	-16	.03	4.32
Temporal region					
Left superior temporal gyrus, BA22	-52	-28	4	.03	3.67
Right superior temporal gyrus, BA22	50	-20	-6	.03	4.22
Left fusiform gyrus, BA37	-48	-60	-14	.03	4.16
Right fusiform gyrus, BA37	38	-58	-16	.03	4.30
Parietal region					
Right parietal cortex, BA40	28	-48	54	.03	3.70
Limbic region					
Left anterior cingulate cortex, BA32	-6	38	18	.03	4.12
Right anterior cingulate cortex, BA32	18	10	46	.04	3.47
Subcortical region					
Corpus callosum	-2	-26	16	.03	4.11

Abbreviations: ASD, autism spectrum disorder; BA, Brodmann area; [¹¹C](R)-PK11195, radioactive carbon-labeled (R)-1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3 isoquinoline carboxamide).

^aThe significance thresholds at the voxel cluster levels were *P* < .05 after false discovery rate correction for multiple comparisons across the whole brain. Coordinates are given in millimeters based on the Montreal Neurological Institute brain template. Each location is a peak within a cluster (defined as the voxel with highest *z* score).

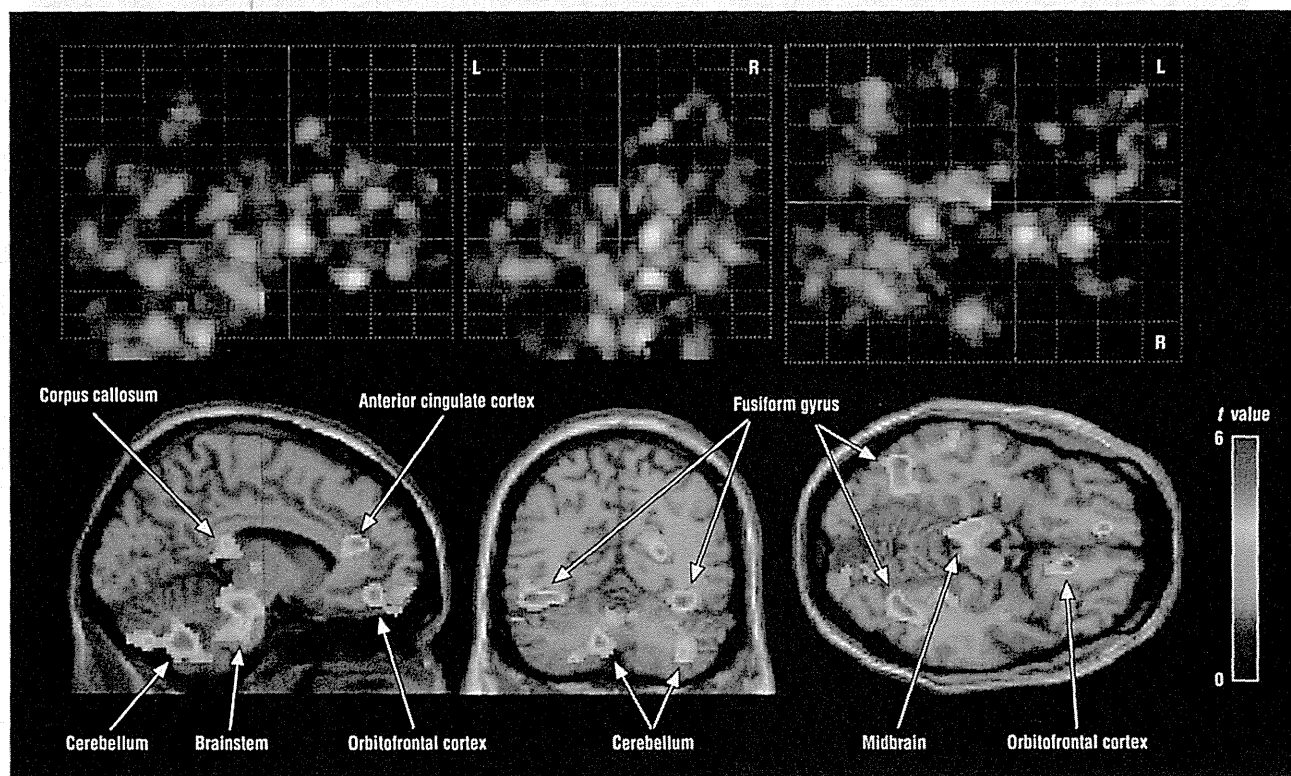


Figure 2. Results of the whole-brain voxel-based statistical parametric mapping analysis of the [¹¹C](R)-PK11195 binding potentials. Locations of clusters with significant increases in the group with autism spectrum disorder compared with the control group (*P* < .05, false discovery rate corrected) are shown on glass brain images and superimposed onto normal-template magnetic resonance images. L indicates left; and R, right.

[¹¹C](R)-PK11195 BPs in 4 VOIs respectively located in the left cerebellum, midbrain, right orbitofrontal cor-

tex, and right anterior cingulate cortex. In the VOI at the left cerebellum, 12 ASD subjects had BPs that were more

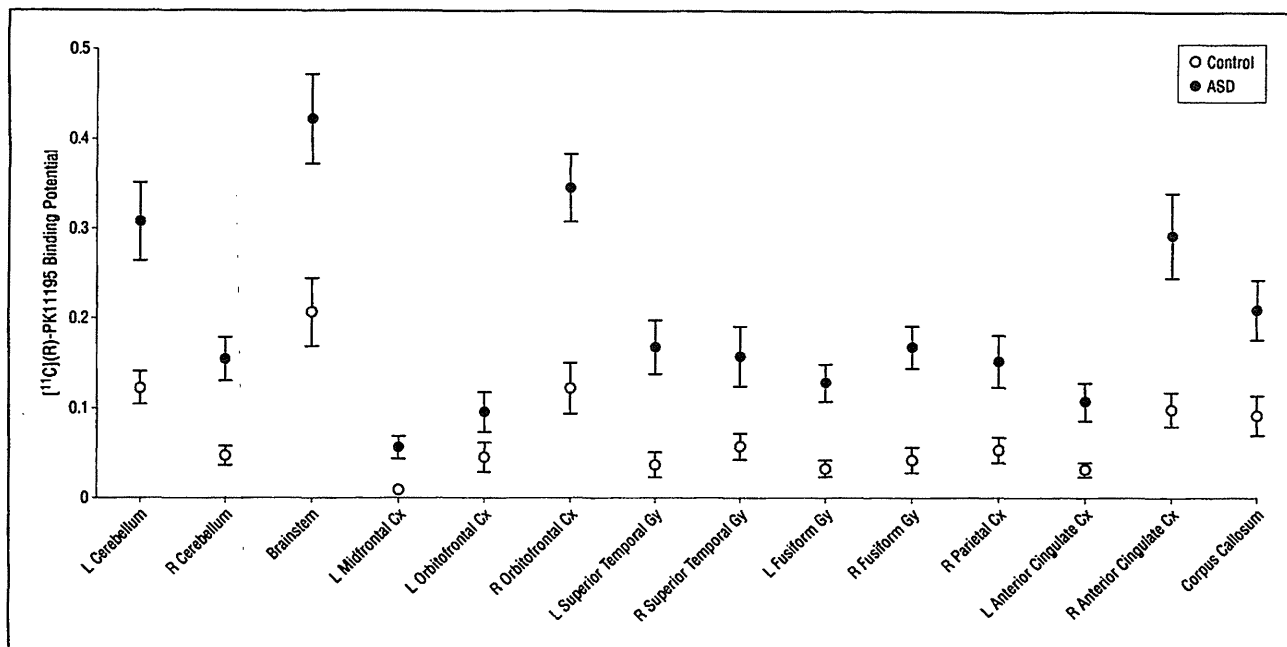


Figure 3. Regional brain [^{11}C](R)-PK11195 binding potential in the autism spectrum disorder (ASD) and control group. Subjects with ASD had significantly higher [^{11}C](R)-PK11195 binding potentials than those of controls ($F_{12,456} = 24.59$, $P < .001$). Error bars represent the SEM. Cx indicates cortex; Gy, gyrus; L, left; and R, right.

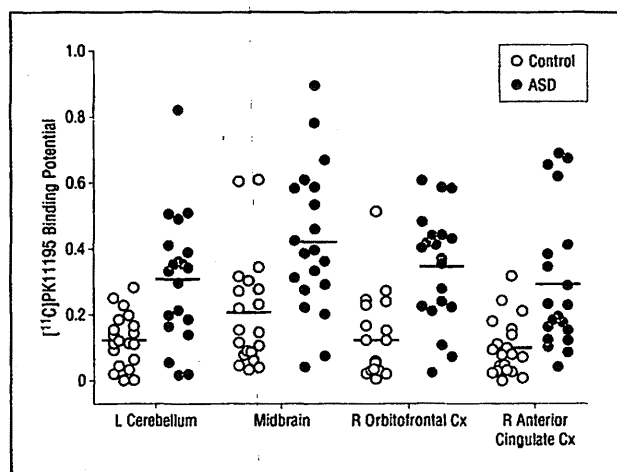


Figure 4. Scatterplot of regional [^{11}C](R)-PK11195 binding potential in the autism spectrum disorder (ASD) and control groups in 4 spherical volumes of interest placed over the left cerebellum, midbrain, right orbitofrontal cortex, and right anterior cingulate cortex.

than 2 SDs higher than the mean BP of controls. The number of ASD subjects who had BPs that were more than 2 SDs higher than the mean value of the controls was 6 for the VOI in the midbrain, 10 for the VOI in the right orbitofrontal cortex, and 8 for the VOI in the right anterior cingulate cortex. Subjects with ASD who exhibited high BPs in at least 3 of the 4 VOIs were classified into a High-BP group ($n = 7$), and the remaining subjects were classified into a Not-High-BP group ($n = 13$). When clinical variables were compared between the High-BP and Not-High-BP groups, statistically significant differences were observed for the social scores of the ADI-R ($U = 19.0$, $P = .04$) and the ADOS ($U = 13.0$, $P = .01$) (**Figure 5**), suggesting that social disabilities might be more severe in the High-BP group.

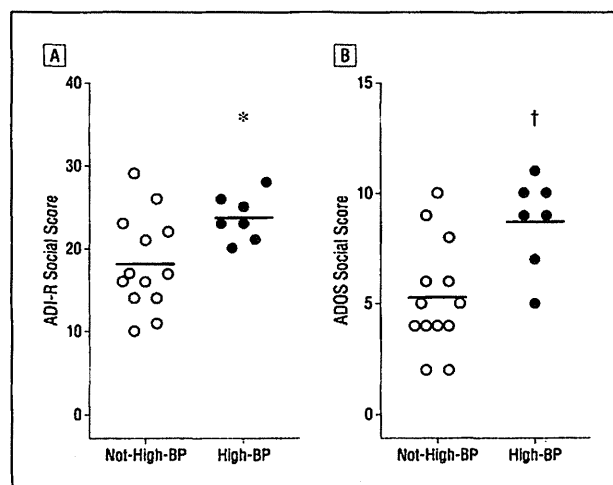


Figure 5. Comparison of social domain scores from Autism Diagnostic Interview-Revised (ADI-R) (A) and Autism Diagnostic Observation Schedule (ADOS) (B) between the High-Binding Potential (BP) and Not-High-BP subgroups in subjects with autism spectrum disorder. * $P = .03$ and † $P = .006$.

COMPARISON OF REGIONAL VOLUME BETWEEN ASD SUBJECTS AND CONTROLS

The absolute volumes of the segmented brain regions were estimated in the control and ASD groups (GM: 676.3 [50.3] vs 705.8 [78.2] [control vs ASD]; WM: 421.7 [42.3] vs 439.7 [48.4]; CSF: 405.1 [47.1] vs 426.0 [50.2]; and intracranial volume: 1503.1 [123.7] vs 1571.5 [161.7]). The multivariate analysis of covariance revealed no significant differences in volume between the 2 groups (GM: $F_{1,37} = 0.006$, $P = .94$; WM: $F_{1,37} = 0.209$, $P = .65$; CSF: $F_{1,37} = 0.036$, $P = .85$). A voxel-wise 2-sample t test analysis of normalized and smoothed