特集2

子どものこころの薬物治療

ADHDに対するアトモキセチンの臨床

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SUMMARY

アトモキセチンの臨床的な印象と，実際の使用経験を，症例を提示してまとめた．メチルフェニデート系の薬物による薬物療法に比較すると，効果発現まで非常に時間が掛かるが，一方で，副作用は比較的軽微であり，継続的な効果が期待できるところが大きな利点である．広汎性発達障害の併存例においても多動を伴う症例には有効性が示されており，また子ども虐待の症例にも，ADHDが基盤となった症例の場合は有効であった．

KEY WORDS

ADHD
アトモキセチン
コンサータ
薬物療法

I. アトモキセチンの薬理効果

アトモキセチンは我が国においては2009年6月に注意欠陥多動性障害（以下ADHD）治療薬として承認を得た新しい薬である．この薬は，従来ADHDの治療薬として用いられてきたメチルフェニデート（リタリン）とは全く異なった作用機序の薬剤であり，メチルフェニデート以外のADHD治療薬としてその意義は大きい．

アトモキセチンは選択的ノルアドレナリン再取り込み阻害剤である．作用機序としてはシナプス前ノルアドレナリン・トランスポーターに選択的に結合し，結果として，シナプス間のノルアドレナリン濃度を高め，強力なノルアドレナリン系の賦活をもたらすと考えられている（表1，図1）．周知の様に，ADHDにおいて，ドパミン系とノルアドレナリン系の機能不全がその大きな要因と考えられており，その点において，ドパミン系の賦活薬であるメチルフェニデートと同様に，病因となる問題に直接作用する薬剤である．一方で，メチルフェニデートとは非常に異なった側面を持つ．

第一に，メチルフェニデートは非常に短期間に代謝をされる薬物であるため，長期的な薬理効果をもたらすためには，複数回の服用か特殊な工夫が必要になる．いうまでもなく，具体的なその形が現在使用され

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ている除放錠に他ならない．一方，アトモキセチンは向精神薬の中でも極めつきに長期型の薬剤である．きちんとした効果を現すまでに，一般的には実に4週間程度を必要とする．しかしこのことは，ひとたび薬理効果が現れれば，終日効果が持続し，薬理効果に関するオン，オフがないことを意味する．

第二に，この様な薬物である為に，メチルフェニデートで問題になった依存性が存在しない．ドパミン系の賦活もメチルフェニデートに比較すれば弱いがアトモキセチンにおいて認められる．しかし，依存性の要因と考えられている報酬系の中枢である側坐核におけるドパミン賦活は認められていない[1]．この点は，安全性という面で大きなプラスになる．

少し脱線であるが筆者としては，メチルフェニデートを巡る臨床的な実感をどうしても述べておきたい．メチルフェニデートの単剤であるリタリンは確かに依存性を気をつけなくてはいけない薬物であり，筆者も常に意識しながら用いてきた．だがその除放剤であるコンサータは，リタリンとは全く別の薬物である．そもそも依存性を作るためには血中濃度が急激に上昇することが前提になる．ジワーっと酔っ払うというお酒が開発されたとして，誰がそれを求めるだろう．他の国に存在しないコンサータへの厳しい登録制は，我が国の子どもの向精神薬におけるガラパゴス島状況を示すものである．

第三に，この様な薬理効果もあって，副作用が軽微で少ない．最も多い副作用は頭痛と食欲不振であるがこの副作用は数週間以内に軽減する場合が多い（表2）．それ以外の長期的な副作用も非常に少ない．このことは，長期的な使用が原則となる，発達障害の子どもに用いられる向精神薬として非常に重要なことである．

最後に，これが最も重要なことではないかと考えられるが，ADHD診断の児童の諸症状に，メチルフェニデートと同等か，あるいはそれ以上のきちんとした治療効果が認められる[2]．アトモキセチンはメチルフェニデート単剤およびその除放剤に比べると，いわゆる切れ味が乏しいと感じる臨床家が多いのではないだろうか．筆者も，当初はそのような印象があった．ところが現在では全く異なった感想を持つようになっ

表2　有害事象：小児を対象とした短期試験

（海外データ）

事象	アトモキセチン群 N=1597 n (%)	プラセボ群 N=934 n (%)	p値[a]
頭痛	300(18.8)	144(15.4)	.035
食欲減退	257(16.1)	39(4.2)	<.001
上腹部痛	211(13.2)	81(8.7)	<.001
嘔吐	168(10.5)	53(5.7)	<.001
悪心	161(10.1)	43(4.6)	<.001
傾眠	139(8.7)	34(3.6)	<.001
疲労	119(7.5)	28(3.0)	<.001
咳嗽	93(5.8)	68(7.3)	.15
易刺激性	88(5.5)	27(2.9)	.002
鼻咽頭炎	88(5.5)	60(6.4)	.38

発現率5%以上の事象でアトモキセチン群の方が多かった有害事象

N=治験薬を1回以上服用した患者　[a]投与群間差のP値，フィッシャーの直接確率検定

※海外データであり，本邦での承認用法用量は異なる

表 1　アトモキセチン：NRI（選択的ノルアドレナリン再取り込み阻害薬）

モノアミントランスポーター	K_i 値
ノルアドレナリン	～ 5 nM
セロトニン	～ 77 nM
ドパミン	～ 1451 nM
その他の神経伝達物質受容体	
ムスカリン受容体	> 2,000 nM
アドレナリン受容体（α及びβ）	> 10,000 nM
ヒスタミン受容体（H1）	> 10,000 nM
ドパミン受容体（D1, D2）	> 10,000 nM
セロトニン受容体（5-HT2）	> 100,000 nM
GABA（GABAA, ベンゾジアゼピン）	≥ 200,000 nM

*K_i 値が小さいほど，受容体親和性が高い

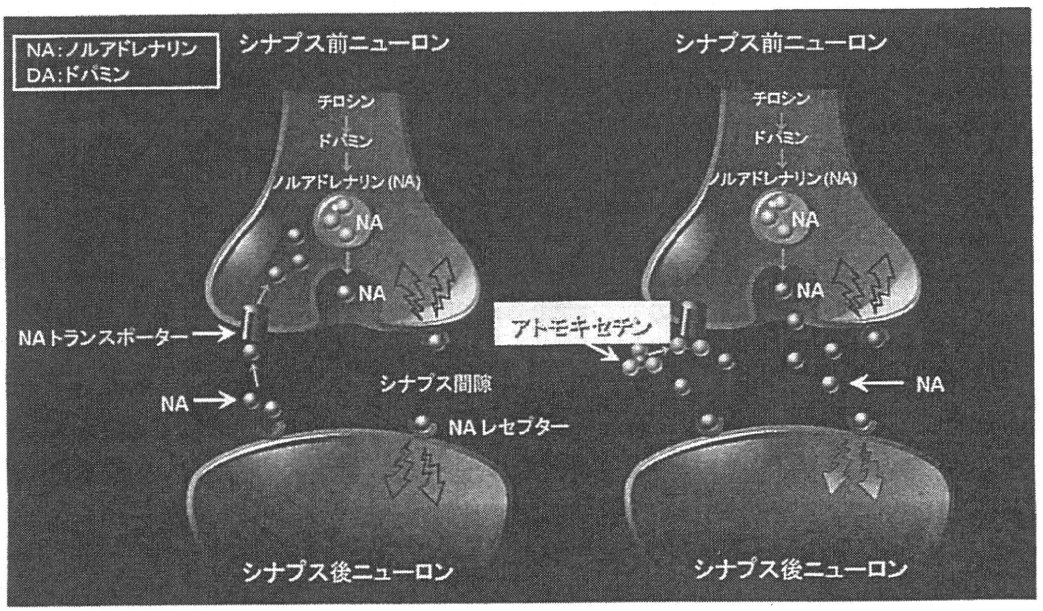

図 1　アトモキセチン：薬理作用
(p.4 カラー図参照)

た．確かに，薬があるのと無いのでは全く別人，といった著効性をアトモキセチンの使用で聞くことは稀である．ところが，実際の学校，家庭での状況をチェックしてみると，著効としかいいようがない変化が現れているのに気付く．

この最後のポイントが最も重要なことではないかと考えられる．印象を伝えるため，経験した症例を数例提示する．なお症例は，いずれも記載の許可を得ているが，匿名性を守るため細部を大幅に変更している．

II. アトモキセチンの実地臨床

筆者がアトモキセチンを使用した症例は30例を超えている．承認されてまだ1年に満たないとはいえ，現在のところ中断例や副作用による中止例がほとんどない．ADHD診断の中にコンサータからの切り替えが数例あり，最も多いものは食欲不振による体重減少によって，家族から薬の切り替えの希望が出され，アトモキセチンの使用を開始したという場合である．

【症例1】 6歳初診，男児，ADHD

母親は感情の起伏が激しく，その母親からはずいぶん叩かれて育ったという．患児の治療の過程で，母親にもカルテを作り並行治療を行った．抑うつと過去のフラッシュバックに対して，抗うつ薬の服用と精神療法を実施した．どうも母親も元多動児であったようだ．

患児は0歳から多動で，始歩と同時にすぐに走り出すなど，幼児期からよく動いた．幼稚園での集団行動は苦手であったが，行事の時に集団で動こうと努力すると，頻尿になったり腹痛を呈したりした．紹介され，6歳にて受診した．診察の結果，社会的な行動の問題は無く，初診時のADHD-RSは不注意素点21点(98%)，多動衝動素点18点（95%），合計素点39点(97%)で，ADHD（混合型）と診断された．

小学校入学後，1学期は何とか問題なく過ごせたが，2学期になると，学校でのけんか，着席の問題などが目立つようになった．このため当初コンサータの服用を開始し，これは著効した．学校でのADHD-RSは不注意素点8点（25%），多動衝動素点8点（50%），合計素点16点（50%）まで改善した．しかし7ヵ月ほど経過したところで食欲不振による体重減少が著しくなった．ちょうどここでアトモキセチンの使用が可能となった為，家族の希望によってアトモキセチンに切り替えた．食欲不振は無くなり，学校での適応も悪化は認められなかった．半年ほど経過した後，父親から，前の薬の方がよく効いていたという印象が述べられたので，学校での様子，家庭の様子について，再チェックを行い，この時点（8歳）でのADHD-RSを取り直してみた．すると家庭での行動評価において，不注意素点7点（50%），多動衝動素点9点（75%），合計素点16点（50%）とほとんど変わらないことが明らかになった．また学校での成績は著しく改善していることも示された．学校でのけんかは時々あり，算数が得意で国語が苦手など学習の教科による得手不得手が認められる．現在の処方は，アトモキセチン25mgである．

この症例は，コンサータからアトモキセチンに切り替えた症例である．両者を用いてみて，印象としてアトモキセチンの切れ味が不良というのは，本人からも時々述べられることである．しかしながら，きちんと評価を行ってみると，実際の効果は大きな差が無いのである．

コンサータからの切り替え例の中に，コンサータを使用してもなお，夕方から夜に掛けて家庭で荒れてしまうという訴えがあり，アトモキセチンに切り替えた症例が存在した．

【症例2】 初診時11歳男児，ADHD，反抗挑戦性障害

父親も元多動児である．患児は3歳頃から多動が目立ち，幼稚園で喧嘩が耐えなかった．集団行動は徐々に向上したが，入学後，1年生では離席が多かった様である．小学校3年生になって，多動は少し治まった．しかし小学校高学年になると授業中座っていることが苦痛になって，学校で注意された時暴れるようになった．同時に家でも暴れる事が増えたが，それに対して父親は暴力的な躾けを繰り返していた．この状態で紹介されて当センターを受診した．切れやすい反面，すごく臆病な所があり夜は1人で2階へ行けないという．

反抗挑戦性障害を伴ったADHDとして治療を開始した．当初，リタリンを用いたが，学校では落ち着くものの午後から不調になり，家での行動は改善しなかった．そのため，夕方に非定型抗精神病薬少量を服用

していた．中学生になると学校では頑張っているがリタリンのリバウンドが著しく，家では著しい苛々が続き，家族の中で孤立し，父親や母親と対立を繰り返すようになった．9月，不登校になった．生活は乱れ，弟や妹への暴力，お金の持ち出しが生じた．12月はついに家出が生じた．ここでコンサータを開始した．コンサータの服用は著効し，登校はスムーズになり，家庭でのトラブルも減った．2年生になると，部活へ熱中する様になり，学校での適応は良いが，夜の不眠がしばしば生じ，眠剤を頓服で使用した．3年生になって受験が迫り，再び家で荒れるようになった．夕方以後に苛々が著しく，朝も不機嫌で再び父親と対立を繰り返すようになった．このため，コンサータからアトモキセチンに切り替えた．父親との対立はその後も続いたが，夕方から翌朝までの荒れた状態は著しく軽減し，無事に志望校への入学を果たすことが出来た．現在の処方はアトモキセチン75mgである．

既にリタリンの使用時から薬理効果のオン，オフで著しい差を示した男児である．アトモキセチンの使用によって，継続した効果を得ることが可能となり，家庭の危機は救われ，患者は高校への進学を果たした．

次の症例は，多動があまり目立たなかったアスペルガー障害の女児である．

【症例3】　初診時6歳女児，アスペルガー障害

母親も広汎性発達障害系の人ではないかと考えられ，地域の学校では少しクレーマー的な母親として，しばしば教師ともめていた．患児は保育園の開始と同時に集団行動の苦手さが目立つようになり，4歳にてアスペルガー障害と診断を受けた．聴覚過敏があり，不意打ちの音に対してパニックを生じ，学校での不適応が著しいということで紹介をされた．

初診時，学校では特定の騒がしい男の子に著しくおびえることがあり，時々不登校を生じていた．小学校2年生になって学習場面で出来ないことがあると，授業中でも泣きわめいてしまい，学習の遅れが目立つようになった．この時点で実施したWISC-IIIでは，特に注意の障害は認められなかった．しかし小学校3年生になって，テスト成績において著しいばらつきが認められ，出来ないときは白紙で出し，一方集中しているときは満点をとるといった状況に筆者は注目した．背後に集中困難があるかもしれないと考え，夏休みにかけてアトモキセチン服用を開始した．2学期になっても忘れものは多く，気分のむらも続いており，母親から見て特に有効性は認められない，と評価された．ところが学校での成績は，2学期になると急上昇し，母親を一驚させた．母親によれば，長文の読み取り，計算など，本人が実は今まで理解できていなかったことが初めて分かったという．学習の著しい改善はその後も進み，学年末に担任教師からは，夏休みを挟み，前半と後半ではまるで別人といわれたそうである．パニックは激減し，3学期には学校が楽しいという言葉も聞かれるようになった．現在の処方はアトモキセチン35mgである．

周知の様に，広汎性発達障害でも多動や不注意を持つグループには，抗多動薬が有効である．筆者にとって非常に興味深かったのは，WISC-IIIにおいて不注意の所見が無かったのにもかかわらず，劇的な効果を示した点である．今まで分かっていなかったことが分かったという母親の言葉は特に印象的であった．

抗多動薬が著効をした児童の中に，被虐待児が何例か含まれる．

【症例4】　初診時5歳男児，ADHD（混合型）

母親は2回の結婚と2回の離婚をし，その後単身で子どもと生活をしていた．夫からのDVがあったという．母親は子ども達に激しい虐待を加えており，患児の目を箸で刺したといった極めて激しい身体的虐待が記録されている．5歳で保護され里親の元で育つようになった．

はじめは会話もままならなかったが，徐々に人との交流が出来るようになった．しかし里親への激しい甘えが生じ，里親の名字を名乗ることに固執し，本名をいわれるとパニックにすらなった．学校が始まると，着席は辛うじて可能であったが，じっと出来ず，他児へのしつこい挑発行為が続き，易怒的で，また会話は一方的だったため，あらためて里親から相談を受け，服薬を開始した．この時点でのADHD-RSは不注意素点25点（99%），多動衝動素点21点（97%），合計素点46点（99%）であった．ごく少量の抗うつ薬と抗精神病薬によって易怒的な状態は幾らか治まったので，知能検査を行った．全IQ82と境界知能であった

が，短期記憶など注意力を反映する下位項目において欠落が認められたため，コンサータの服用を開始した．薬物療法は著効し，はじめて座って課題に取り組めるようになった．しかしその後も，ハイテンションになって，フラッシュバックがひどくなり，急にかんしゃくを起こして暴れ，その後ぼーとなってしまうといった状況が数ヵ月置きに生じていた．7歳，食欲不振が強くなったので，コンサータをアトモキセチンに変更した．その後，フラッシュバックの波が非常にあるので，さらに加えて桂枝加芍薬湯と四物湯を3ヵ月ほど服用したところ，落ち着きが非常に良くなった．8歳になって，お化けの気配はまだするといっているが，学習にはきちんと取り組めていて，情緒的にも安定している．現在の処方は，アトモキセチン25mg，リスペリドン0.3mg，カルバマゼピン30mg，桂枝加芍薬湯1包である．

子ども虐待による反応性愛着障害と解離を背後に持つ多動性行動障害と，ADHDとは非常に鑑別が難しい問題である[3]．前者は西澤[4]によればADHD様症状としてADHDからは分けることが必要と指摘されているが，子ども虐待が絡むADHD診断のグループにはどうやら二種類あり，ADHDの基盤があって，そのADHDも要因になって子ども虐待が加算されたという症例と，比較的重症の愛着障害で西澤のいうADHD様症状が生じたと考えられる症例とが共に認められる．そして前者に関しては，抗多動薬の服用がきちんと効くのである．ただし抗多動薬だけでは状態改善には不足で，症例に示すように，抗精神病薬および気分調整薬，対フラッシュバック薬などの併用が必要である．

もう一つ，我々は2例ほど児童期の双極性障害と考えられる症例に対して，アトモキセチンが著効という経験をした．同様の症例報告[5]が既になされているが，ADHDと双極性障害との関連もまた大きな論議になっている．この様な例に関しては，薬理効果がきちんと説明が出来ない．ただ単に，そういう例があったと今のところいうほかは無い．

III. アトモキセチンの使用が勧められる症例とは

アトモキセチンにおいて，最も大きな有利な点は，症例2や症例4に見るように，継続的で持続的な効果を示すことであろう．さらに余り効果があったとは見えないのに，実は有効であったという奇妙な効き方をする場合があることも，症例3において示した．まるで漢方薬である．最も大きな不利な点は，有効性を発揮するまでに時間がかかることである．せっかちで多動なADHDの家族と，同じ傾向を持つ小児科医が4週間という時間を待てるかどうかが一つの鍵になるのではないかと思う．しかし有効性が発揮できるまできちんと服用が可能であれば，継続的な効果は大きな利点になる．

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Determining differences in social cognition between high-functioning autistic disorder and other pervasive developmental disorders using new advanced "mind-reading" tasks

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ABSTRACT

Deficits in understanding the mental state of others ("mind-reading") have been well documented in individuals with pervasive developmental disorders (PDD). However, it is unclear whether this deficit in social cognition differs between the subgroups of PDD defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. In this study, PDD was divided into high-functioning autistic disorder (HFA) ($n = 17$) and other PDD ($n = 11$) consisting of Asperger's disorder ($n = 8$) and PDD-NOS ($n = 3$), and differences in mind-reading ability was examined between the two clinical groups and controls ($n = 50$) using a new advanced naturalistic task consisting of short scenes from a TV drama showing communication in social situations. The task was divided into visual and auditory tasks to investigate which modality was more valuable for individuals with PDD to understand the mental state of others. The results suggest that social cognition differs significantly between individuals with HFA and those with other PDD, with no difference being found between those with other PDD and controls. Neither the auditory or visual modality was found to be dominant in subjects with PDD in the mind-reading task. Taken together, complex mind-reading tasks appear to be effective for distinguishing individuals with HFA from those with other PDD.

1. Introduction

The term "theory of mind (ToM)", which describe the ability to attribute mental states to oneself or another person, was introduced in psychology by Premack and Woodruff (1978). Since Baron-Cohen, Leslie, and Frith (1985) first reported "deficit of ToM" in which the autistic condition is seen as a failure to attribute mental states to others, much work has been conducted on ToM in pervasive developmental disorders (PDD). The ability to understand the mental state of others, which underlies fundamental social skills, is also referred to as "mind-reading" (Baron-Cohen et al., 1985). The basic ToM test,

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usually consisting of the first and the second-order false belief tasks, is not sufficiently complex to detect deficits in adults with high-functioning PDD (HFPDD) (Bowler, 1992; Happé, 1994; Ozonoff, Pennington, & Rogers, 1991). Thus, an advanced ToM test, the Strange Situation Test, was devised by Happé (1994) in which participants are asked to provide an explanation for non-literal statements (e.g. irony or lie) made by story characters. Happé's study demonstrated that participants with PDD who passed the first and second-order false belief tasks did show specific deficits in ToM on this more complex test.

Many advanced ToM studies were subsequently conducted with adults with HFPDD in order to investigate subtle deficits of "mind-reading" ability. The Eyes Test was created for adults with HFPDD as a mind-reading task that uses information from the visual modality alone (Baron-Cohen, Wheelwright, & Jolliffe, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). In the task, participants are shown photographs in which only the areas of the eyes are cut out from a person's face, and they are asked to identify the person's mental state. Researchers have revealed that individuals with PDD provide less correct justifications of mental state than controls, indicating that the Eyes Test is highly accurate in measuring mind-reading ability. However, in the real world, in order to integrate all of the information which people express, we look not only at the eyes of others, but also at their facial expressions, body language, posture and so forth. Moreover, we do not look at a static face and body in the real world, but at a moving face and body. Thus, a task that presents dynamic information in both the visual and auditory modality, such as video, was deemed to be more realistic and was expected to measure the ability to understand others' mental states in daily life. Accordingly, Heavey, Phillips, Baron-Cohen, and Rutter (2000) developed the "Awkward Moments Test" which uses scenes taken from TV programs and commercials and Roeyers, Buysee, Ponnet, and Pichal (2001) devised the "Empathic Accuracy Task" which uses recordings of real communicative interactions. In their studies, participants viewed moving images (video) and tried to determine the mental states of the characters. Participants with PDD provided less correct justifications of mental state than typically developing subjects.

More recently, a question has been raised about which of the auditory and visual modality is more valuable for adults with PDD to understand the mental state of others. A task that extends the abovementioned advanced tasks into the auditory modality was created by Rutherford, Baron-Cohen, and Wheelwright (2002), and a study employing this task with adults with Asperger's disorder (AS) and high-functioning autistic disorder (HFA) revealed that both groups had difficulty extracting mental state information from vocalizations (Golan, Baron-Cohen, Hill, & Rutherford, 2007). In addition, use of the Cambridge "Mind-Reading" (CAM) Face-Voice Battery in adults with AS to test their cognition of 20 complex emotions and mental states from faces or voices (Golan, Baron-Cohen, & Hill, 2006) showed that although the participants showed deficits in social cognition when relying on either facial or vocal information alone, they could understand others' mental state better from the voices than from the faces. Given this finding among individuals with AS, one of the objectives of the present study is to identify which modality—visual (facial expression, gesture and posture) or auditory (pitch, intonation and tone of speech)—is more valuable for adults with PDD to understand the complex emotions of others.

Most recent studies using the advanced mind-reading tasks with moving stimuli have treated adults with PDD as one group. Some earlier studies, however, investigated the difference in mind-reading ability between the subgroups of PDD, especially between HFA and AS, but still today it is unclear whether in fact the two disorders differ in degree of impairment of mind-reading ability (Dahleger & Trillingsgaard, 1996; Ozonoff, Rogers, & Pennington, 1991; Ozonoff, South, & Miller, 2000; Zaitai, Durkin, & Pratt, 2003). A recent study that compared the subgroups of HFA and AS with typically developing adults was conducted by Spek, Scholte, and Van Berckelaer-Onnes (2010), who used the Eyes Test (Baron-Cohen et al., 1997), the Faux Pas Recognition Test (Stone, Baron-Cohen, & Knight, 1998) and the Strange Stories Test (Happé, 1994). The findings suggested that there was no significant difference in mind reading ability between individuals with HFA and AS on any of the tasks. However, since Spek et al. did not employ the CAM or moving images in their mind-reading task, it remains to be determined whether mind-reading ability differs on a more complex, moving mind-reading task between the PDD subgroups.

Thus, the second objective of the present study was to clarify whether any differences exist in mind-reading ability between HFA, a typical PDD, and other PDD consisting of AS and pervasive developmental disorder not otherwise specified (PDD-NOS). We hypothesized that individuals with HFA would show greater deficits in mind-reading ability than those with other PDD.

2. Methods

2.1. Participants

The clinical group comprised 28 male adolescents and adults with PDD (mean age 24.5 years, SD = 7.7 years, range = 16–45 years). Participants were recruited from a private child psychiatric clinic specializing in PDD or a research volunteer pool of the PDD research group at the National Institute of Mental Health. All participants were diagnosed by experienced child psychiatrists. The diagnostic process was conducted by a team of one child psychiatrist and one or two clinical psychologists. The psychiatrist interviewed the parents about their child's developmental history and daily behaviors. In parallel, in another room, the clinical psychologist observed the social behavior and communication of each participant during the IQ test and in conversation which included questions about daily life, their community and interpersonal relationships. Based on the data obtained, the participants were diagnosed according to the established criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (APA, 2000): 17 were diagnosed with HFA (showing qualitative impairment in social interaction, qualitative impairment in communication, and restricted repetitive and stereotyped patterns of behavior, interests, and activities), and 11 were diagnosed with other PDD, which combined 8 participants with

Table 1
Descriptive characteristic of participants.

	HFA[a] ($n = 17$)			Other PDD[b] ($n = 11$)			Control ($n = 50$)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Chronological age	24.2	8.5	16–45	25.0	6.6	17–35	19.3	1.7	18–22
Full Scale IQ	103.2	13.5	87–132	108.2	9.7	88–119			
Verbal IQ	103.9	14.5	80–136	109.4	10.1	83–120			
Performance IQ	100.3	16.7	72–126	106.5	16.4	66–127			
AQ[c]	33.3	6.5	24–44	33.6	6.3	28–44			

[a] High-functioning autistic disorder.
[b] Pervasive developmental disorders.
[c] Autism Spectrum Quotient.

AS and 3 participants with PDD-NOS (showing atypical autistic symptoms that are relatively mild and do not meet the diagnostic criteria of the main symptoms of Autistic disorder). Also, 14 participants were tested using the Wechsler Adult Intelligence Scale Reversed (WAIS-R), 3 were tested using the WAIS-Third Edition (WAIS-III), and 11 were tested using the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (Wechsler, 1981, 1991, 1997). The characteristics of the participants with PDD are shown in Table 1. All participants had a full intelligence quotient (FIQ) of at least 85. In addition, all participants except one were administered the Autism Spectrum Quotient (AQ)-Japanese version (Wakabayashi, Baron-Cohen, Wheelwright, & Tojo, 2005). No significant differences in FIQ ($t = 1.1$, $p = .30$), the verbal intelligence quotient (VIQ) ($t = 1.1$, $p = .29$), the performance intelligence quotient (PIQ) ($t = 1.0$, $p = .35$) and AQ ($t = .18$, $p = .90$) scores were found between the HFA group and other PDD group. The participants had no other psychological diagnosis.

The control group consisted of 50 male students recruited from the University of Chiba (mean age 19.3 years, SD = 1.74). They were no administered IQ tests, but on the basis of their grade level it was assumed that they had normal intelligence.

Written informed consent to participate in the study was obtained in advance from all participants and from their parents when the participants were minors (<20 years of age), and the study protocol was approved by the Ethics Committee of the National Institute of Neurology and Psychiatry.

2.2. Instruments

2.2.1. Visual and auditory tasks

We administered the Motion Picture Mind-Reading (MPMR) Task, which was originally designed to measure individual differences among adults in the general population (Wakabayashi & Katsumata, in press). The MPMR consists of short clips from the TV drama "*Shiroi Kyotou*" (Kobayashi, 1978), which was famous in the 1970s but would not be well known to the younger participants in this study. The storyline concerns malpractice at a famous medical school in Japan. The drama was edited into clips using DVRaptor software (Canopus Company, Japan). The length of each of the 41 scenes ranged from 3 s to 11 s (mean 5.2 s). The MPMR Task thus contained more realistic material than the ToM tasks used in previous studies because it contained scenes from dramatized real life. Moreover, the content was highly complex, including many non-literal scenes with incongruent dialogue and mental states conveying, for example, characters who were lying or being ironic. The participants were asked to understand the hidden intent, masked behind incongruent visual information (facial expression, gesture and posture) and auditory information (the non-literal aspects of speech of pitch, intonation and tone).

In order to identify whether the visual or auditory modality was more valuable for adults with PDD to understand the complex mental states of others, we modified the 41 clips of the MPMR to create one visual task and one corresponding auditory task for each clip. For the visual task, the sound was edited out of each scene. For the auditory task, no picture was displayed on the PC monitor and only the auditory stimuli composed of segments of the one character's speech was heard (see Fig. 1). In each of the visual and auditory trials, participants had to decide whether a label appearing on the PC monitor described the character's mental state (intent) appropriately or not. Of the 41 clips, 27 were labeled correctly and 14 incorrectly (Table 2).

2.2.2. Autism Spectrum Quotient-Japanese version (AQ-Japanese version)

The AQ is a self-report questionnaire which measures the degree to which any adult of normal IQ possesses traits related to the autism spectrum (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). The AQ-Japanese version (Wakabayashi et al., 2005) was used in this study.

2.3. Procedure

The participants were tested individually in a quiet room at the clinic or university. Both the visual and auditory task stimuli were presented to the participants while were wearing headphones. The clinical groups viewed the stimuli on a 13.3-in. monitor of a laptop computer running Windows XP (Dynabook SS MX/190DR, Toshiba), while the control group viewed them on a 17-in. PC monitor (Dimension XP 4400, Dell). The participants' response to each item was recorded by computer. Each task began with the message "To start, press the space key". After 1 s, the stimuli were presented in either the visual or

Fig. 1. Example of the test stimuli used in the visual task without auditory information (Scene 1, Feigning). In the auditory task which presented the dialogue, "Um, I just feel like seeing you, big brother" there was no picture of the character displayed on the screen. In each of the visual and auditory trials, participants had to decide whether the label appearing on the screen described the character's mental state (intent) appropriately or not.

auditory modality scene accompanied by the word or phrase describing a mental state. The participant was asked to judge whether the word or phrase presented on the screen described the person in each scene appropriately or not. To record their judgment, they pressed the F key to which was attached a small label saying "appropriate" or the J key to which was attached the label "inappropriate". One second after participants pressed a key, a message appeared saying "Next scene, press the space key", and as a participant pressed it, the next trial started. The presentation order of the 41 clips was randomized for each participant.

Participants completed one practice trial for one visual and one auditory task before the experiment started. The order of the visual and auditory tasks was counterbalanced. Throughout the entire test, a task requiring the participants to determine the camera angle from which a photo was taken was inserted between the Visual tasks and the Auditory tasks to serve as interference stimuli.

3. Results

3.1. Comparison of groups by diagnosis

Accuracy rate was determined by two-way repeated measures ANOVA. The main effect of Group was significant: the HFA group had a lower accuracy rate than the other PDD and control groups. The main effect of Task was also significant in all three groups. The interaction between Group and Task was not significant ($F(2,75) = 0.2$, $P = 0.80$).

The accuracy rate for each task modality is shown in Fig. 2. ANOVA revealed significant main effects for Task ($F(1,75) = 19.0$, $P < 0.01$) and Group ($F(2.75) = 7.9$, $P < 0.01$). The accuracy rate was higher on the visual task than on the auditory task in all groups. The interaction between Task and Group was not significant ($F(2,75) = 0.2$, $P = 0.80$). Results of Bonferroni multiple-comparison tests showed that the accuracy rate of the HFA group was lower than that of the control group ($P < 0.01$) and the other PDD group ($P < 0.05$). No significant difference was found between the other PDD and control groups.

3.2. Within-group comparisons of accuracy rate

No correlations were found for the HFA group and other PDD group with respect to the accuracy rates on the visual task and auditory task, and FIQ, VIQ, PIQ and AQ scores.

3.3. Between-group comparisons of accuracy rate

The accuracy rates on the visual task and auditory task (41 items each) were compared between the HFA, other PDD, and control groups using Fisher's exact test. As shown in Table 2, significant differences were observed for some items on the Visual and Auditory task.

4. Discussion

This study investigated differences in mind-reading performance among PDD subgroups by using advanced mind-reading tasks comprised of clips from a TV drama that included social context in the form of another character appearing and

Table 2
Accuracy rate for determining the character's mental state among the three subgroups of PDD.

Scene	Duration (s)	Word/phase shown on screen	Visual				Auditory			
			HFA[a] ($n = 17$)	Other PDD[b] ($n = 11$)	Control ($n = 50$)	p	HFA ($n = 17$)	Other PDD ($n = 11$)	Control ($n = 50$)	p
1	3	Feigning	53	64	72	.35	94	82	82	.47
2	3	***Respectful***	35	73	82	.00**	65	64	76	.54
3	6	Sarcastic	71	73	82	.55	59	55	52	.89
4	7	Ironic	82	100	88	.36	71	46	46	.20
5	6	***Pleased***	30	64	48	.19	38	30	14	.10
6	3	Disbelieving	65	82	60	.39	65	82	70	.62
7	4	***Convinced***	47	73	80	.03*	82	91	92	.52
8	9	***Confident***	35	55	74	.01*	29	55	70	.01*
9	6	Bluffing	82	82	72	.61	77	82	82	.88
10	3	Ingratiating	65	64	62	.98	71	80	74	.87
11	6	Astonished	88	82	74	.45	71	73	48	.13
12	3	Feigning	82	91	76	.51	63	100	76	.08
13	4	Pretending not to want	77	82	64	.39	12	27	28	.39
14	9	Ironic	77	90	86	.56	65	73	72	.84
15	9	Sarcastic	59	73	92	.01*	53	55	66	.56
16	4	Playing down	82	82	58	.10	53	91	86	.01*
17	5	Coercive	65	73	68	.91	56	64	88	.01*
18	9	***Worried***	82	100	82	.31	65	46	62	.55
19	6	Lying	41	64	72	.07	71	55	72	.52
20	4	Ironic	88	64	74	.30	59	64	84	.07
21	4	Guilty	41	91	86	.00**	41	91	62	.03*
22	3	Sarcastic	41	64	64	.24	47	82	68	.14
23	9	Ingratiating	41	64	52	.50	81	91	88	.72
24	3	***Appreciative***	29	91	84	.00**	35	73	62	.09
25	4	Feigning	53	73	82	.60	88	82	88	.85
26	5	***Wondering***	77	64	82	.40	18	36	50	.06
27	9	***Praising***	24	27	46	.18	29	36	38	.82
28	3	Angry	82	73	90	.29	59	73	86	.06
29	5	***Mocking***	24	18	30	.68	12	10	32	.13
30	3	***Disappointed***	77	46	68	.22	47	55	60	.64
31	11	Figuring someone out	41	91	46	.02*	53	82	68	.27
32	4	***Unsure how to react***	47	55	78	.04*	35	36	48	.58
33	3	Employing tactics	82	73	86	.56	69	100	78	.14
34	7	Flattering	82	82	92	.43	59	55	40	.34
35	7	Teasing	65	73	46	.16	77	64	70	.76
36	6	***Apologetic***	77	73	96	.02*	29	72	78	.00**
37	5	Covering up Embarrassed	71	100	82	.14	53	64	68	.54
38	7	***Not liking***	65	73	86	.14	41	36	58	.28
39	5	Modest	88	91	92	.90	71	90	84	.36
40	7	Sarcastic	77	46	56	.21	59	73	78	.31
41	9	***Ashamed***	31	36	62	.05*	47	80	86	.00**

Note: Words/phrases not appropriate to the scene are shown in bold italics. Items shown in yellow highlight are under chance level of the control group. Fisher's exact test, $^{*}p < .05$, $^{**}p < .01$.

[a] High-functioning autistic disorder.

[b] Pervasive developmental disorders.

background scenery being visible. According to Adolphs, Sears, and Piven (2001) and Golan et al. (2006), compared to recognizing general emotions, it is difficult for adults with PDD to recognize the intentions and emotions underlying facial expressions that do not correspond with speech. All of the task items in the present study were designed to assess participants' understanding of hidden emotions and mental states that do not concord with the language heard, and these items were thus expected to present some difficulty for adults with PDD. While differences were observed between the HFA group and control group and between the HFA group and other PDD group, no differences were observed between the other PDD group and control group. This finding suggests that a close relationship exists between cognitive ability, which is closely connected with social communication such as mind-reading ability, and the behavioral characteristics of PDD as laid out in the DSM diagnostic criteria. These findings replicate those of previous ToM research studies which showed that the differential abilities in ToM may help to distinguish AS from autism (Ozonoff, Rogers, et al., 1991; Zaitai et al., 2003).

As to differences in mind-reading ability between the subgroups of PDD, Spek et al. (2010) previously reported no such difference between subjects with HFA and AS. The contradictory results of our study and theirs might be due to the different format of the tasks used. More specifically, the tasks used in their study might not be able to detect the subtle differences in mind-reading performance between the HFA and AS subgroups. Golan et al.'s (2006) comparative study of individuals with AS and those with typical development which used the CAM reported significant differences in performance on both the

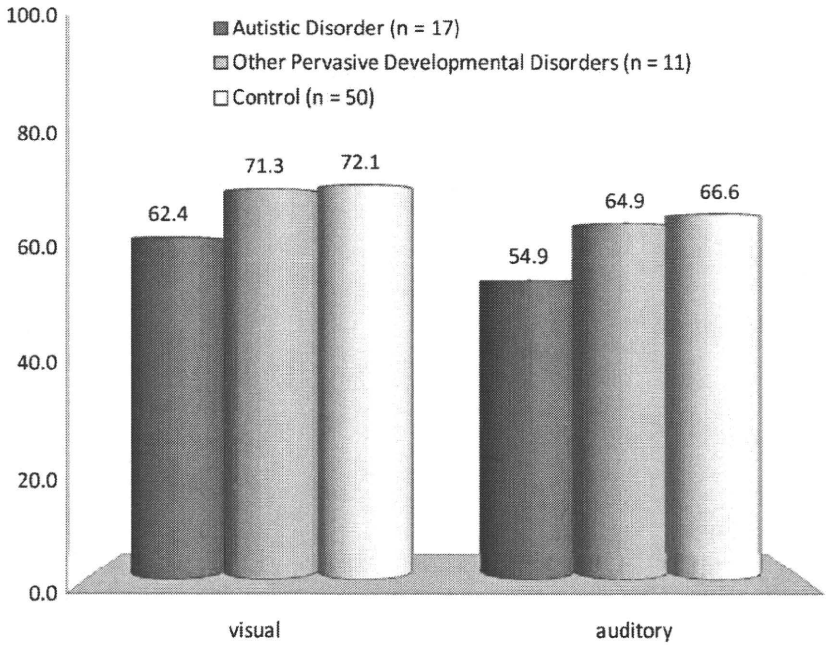

Fig. 2. Mean accuracy rate on the visual and auditory tasks for each group.

visual and auditory tasks, findings which do not accord with those of the present study. The reason for the discrepancy might be attributable to the inclusion of social context in the MPMR clips, where, for example, two characters can appear together on screen or background scenery can be visible. Also the participants' response method differed between the two studies: while Golan et al. (2006) asked participants to select a word from 4 alternatives to describe an appropriate mental state matching facial expression and voice, we asked them to judge whether a word describing a mental state was appropriate or not to the scene.

The present finding that individuals with other PDD showed accuracy rates close to those of the control group suggests that adults with other PDD might understand other people's minds to some extent. However, in everyday life, their social communication is often not successful, which could suggest that even though they may understand other people's mental states, they might experience difficulties responding to them. Moreover, previous studies have shown that individuals with PDD rely on strategies different from those of the general population when trying to understand others' thoughts and emotions (Baron-Cohen et al., 1999; Castelli, Frith, Happé, & Frith 2002; Happé et al., 1996). Future studies of the brain by, for example, functional magnetic resonance imaging might reveal the difference in strategies adopted by individuals with other PDD and controls.

The present study found no correlation between FIQ, VIQ and PIQ scores and task performance in the HFA and other PDD groups. A previous study by Happé (1995) showed that VIQ score was correlated with mind-reading ability, whereas in the present study there was no such relation between VIQ score and performance. This is because all participants had an IQ $\geq$80, and therefore differences in VIQ score were small among the PDD subgroups. Moreover, there was no correlation between AQ score and task performance. A high AQ score indicates serious symptoms of autism, alongside which lower mind-reading task performance would be expected. The finding therefore suggests that mind-reading ability might be associated with symptom profiles that are in accordance with the diagnostic criteria of DSM-IV-TR, rather than degrees of autism as assessed by AQ scores.

Regarding test items that showed significant differences in accuracy rate between the three groups, the HFA group had lower accuracy on most of the visual and auditory tasks than the other PDD and control groups. Contrary to expectation, the accuracy rate of the HFA group for some items was under the chance level (50%) of the control group, and the other PDD group showed a higher accuracy rate than the control group on several items, including "figuring someone out" on the visual task and "guilty" on the auditory task. Moreover, the HFA group showed a higher accuracy rate than the control group on a few items. We suspect that some emotions and mental states are relatively easier for adults with PDD to understand, based on their previous experiences. This remains a subject for further investigation.

With respect to the objective of determining whether there exist differences in the mind-reading performance according to whether the visual or auditory modality is used, we found no such differences. These findings are contrary to those of Golan et al. (2006) who found that males with AS perform better on the auditory task than on the visual task, which suggests that there may be no difference in understanding of others' mind by modality. The reason for this may be attributable to the complexity of the tasks and language used, or cultural differences between the two experimental settings. In general, Japanese people make less obvious facial expressions than Western people, and as such, cultural differences might have produced differences in the results.

A limitation of this study is that the group of PDD participants was small, as then was the two subgroups. Therefore, future study should involve a larger number of participants. In addition, the profiles of the control group participants lacked important information. For example, no accurate IQ information was available, although because the average IQ of the PDD group participants was higher than 100 and no correlation was found between IQ and mind-reading performance, the influence of IQ appears to be limited. In future studies, the IQ, age and education level of the control group should be matched to those of the PDD group. Moreover, the participants in this study were all male. Given that gender differences on mind-reading tasks have been reported (Baron-Cohen, Wheelwright, Skinner, et al., 2001; Baron-Cohen, 2003; Golan et al., 2006; Rutherford et al., 2002; Wakabayashi & Katsumata, in press), future work should include female participants. Finally, the tasks used in this study were created from clips from a TV drama, which resulted in somewhat uncontrolled categories of emotions. Thus, future use of controlled categories of emotions to examine performance differences among groups divided by diagnosis should contribute to identifying those emotions and mental states that are relatively easier for adults with HFA to recognize.

5. Conclusions

Using the new visual and auditory tasks, this study compared the performance of subgroups of PDD divided according to DSM-IV-TR diagnostic criteria in order to clarify the difference in mind-reading abilities among the subgroups. The results demonstrated that on both the visual and auditory tasks, individuals with HFA experienced the greatest difficulty in understanding the complicated emotions and mental states of others. In contrast, the results suggest that the mind-reading abilities of adults with AS and PDD-NOS did not differ much from those without PDD. Taken together, complex mind-reading tasks appear to be effective for distinguishing individuals with HFA from those with AS or PDD-NOS. Clinically, adults with HFA who are not able to understand easily others' thoughts and emotions will likely encounter problems in social relationships. Individuals with AS or PDD-NOS will likewise experience such problems, but for different reasons: although they might well be able to understand others' emotions and thoughts, they will likely have difficulty knowing how to adapt their own social behavior. The support offered to individuals of different PDD subgroups may need to be differentiated accordingly.

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ORIGINAL ARTICLE

Reduced Acetylcholinesterase Activity in the Fusiform Gyrus in Adults With Autism Spectrum Disorders

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Context: Both neuropsychological and functional magnetic resonance imaging studies have shown deficiencies in face perception in subjects with autism spectrum disorders (ASD). The fusiform gyrus has been regarded as the key structure in face perception. The cholinergic system is known to regulate the function of the visual pathway, including the fusiform gyrus.

Objectives: To determine whether central acetylcholinesterase activity, a marker for the cholinergic system, is altered in ASD and whether the alteration in acetylcholinesterase activity, if any, is correlated with their social functioning.

Design: Using positron emission tomography and a radiotracer, *N*-[^{11}C]methyl-4-piperidyl acetate ([^{11}C]MP4A), regional cerebrocortical acetylcholinesterase activities were estimated by reference tissue–based linear least-squares analysis and expressed in terms of the rate constant k_3. Current and childhood autism symptoms in the adult subjects with ASD were assessed by the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview–Revised, respectively. Voxel-based analyses as well as region of interest–based methods were used for between-subject analysis and within-subject correlation analysis with respect to clinical variables.

Setting: Participants recruited from the community.

Participants: Twenty adult subjects with ASD (14 male and 6 female; age range, 18-33 years; mean [SD] intelligence quotient, 91.6 [4.3]) and 20 age-, sex-, and intelligence quotient–matched healthy controls.

Results: Both voxel- and region of interest–based analyses revealed significantly lower [^{11}C]MP4A k_3 values in the bilateral fusiform gyri of subjects with ASD than in those of controls ($P < .05$, corrected). The fusiform k_3 values in subjects with ASD were negatively correlated with their social disabilities as assessed by Autism Diagnostic Observation Schedule as well as Autism Diagnostic Interview–Revised.

Conclusions: The results suggest that a deficit in cholinergic innervations of the fusiform gyrus, which can be observed in adults with ASD, may be related to not only current but also childhood impairment of social functioning.

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AUTISM SPECTRUM DISORDERS (ASD), comprising autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified, are characterized by impairment in both social interaction and communication as well as by restricted or repetitive behaviors and interests.[1] Although individuals with ASD also have significant deficits in face perception,[2,3] this aspect is not included in the current diagnostic criteria.[1] Because of the fundamental role of face processing in social interactions, it has been hypothesized that abnormalities in the neural circuitry involved in face processing contribute to social disabilities in ASD.

It is well recognized from functional magnetic resonance imaging (fMRI) studies that a specific region of the fusiform gyrus called the fusiform face area (FFA) is consistently active during face viewing in typically developing individuals.[4,5] The FFA activity in face processing is known to be dominated by the right hemisphere,[6] and the functional volume of the right FFA, defined by fMRI during face viewing, may increase with age.[7] Most previous fMRI studies have found that subjects with ASD lack FFA activation in response to strangers' faces,[8-10] although subsequent studies have shown that differences in FFA activation between typically developing and autistic people may

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be mediated by task demand,[11,12] familiarity,[13,14] or the amount of time spent fixating on the eyes.[15] The FFA hypofunction, especially in the right hemisphere, that occurs when children and adults with ASD view strangers' faces, is the best-replicated fMRI abnormality.[14,16] This phenomenon may arise from neuropathological abnormalities in the fusiform gyrus in ASD; in a recent postmortem study by van Kooten et al,[17] compared with controls, patients with autism showed significantly lower neuron densities in layer III, total neuron numbers in layers III, V, and VI, and mean perikaryal volumes of neurons in layers V and VI in the fusiform gyrus.

Several neurotransmitters including acetylcholine, dopamine, noradrenaline, and serotonin have been found to play important roles in cortical activity.[18,19] In the visual cortex, acetylcholine makes the greatest contribution to the biophysical properties of the neurons and synaptic efficacy, although the involvement of noradrenaline and serotonin is also implicated.[19] Evidence of the critical effect of acetylcholine on fusiform activity has been derived from the results of fMRI and positron emission tomography (PET) studies, which have demonstrated that pharmacological manipulation of cholinergic activity can alter the function of the fusiform gyrus; scopolamine reduced fusiform activity in individuals who performed a long-term encoding task,[20-23] while cholinergic enhancement by the cholinesterase inhibitor physostigmine augmented the relative neuronal response in the middle fusiform gyrus during emotional processing.[24] These findings suggest that abnormalities in cholinergic function could occur in the fusiform gyrus in individuals with ASD and that such abnormalities would be associated with social disability. To test this hypothesis, we assessed acetylcholinesterase (AChE) activity, a marker for the central cholinergic system,[25] in adult individuals with ASD and age- and sex-matched controls by PET and the radioactive tracer *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A), which is an analog of acetylcholine and is selectively hydrolyzed by AChE.[26,27] Furthermore, we examined the clinico-biomarker relationship by comparing clinical variables with regional [^{11}C]MP4A PET data in subjects with ASD. Because previous studies describe right-hemisphere dominance in fusiform hypofunction during face processing[14,16] and unaltered choline acetyltransferase activities in the postmortem parietal and frontal cortices[28] in autism, we predicted that abnormalities in AChE activity measured by [^{11}C]MP4A PET would be less prominent or not altered in the cerebral cortex, other than the right-hemisphere fusiform gyrus, in subjects with ASD.

METHODS

SUBJECTS

Twenty subjects with ASD (14 male and 6 female; mean [SD] age, 23.5 [4.3] years; age range, 18-33 years) and 20 age- and sex-matched control subjects (14 male and 6 female; mean [SD] age, 23.1 [4.2] years; age range, 19-34 years) participated in this study. All of the participants were right-handed and had an intelligence quotient greater than 70. None of the participants were tobacco smokers or taking any medication, including psychotropic drugs. All of the subjects with ASD were diagnosed by 2 trained child psychiatrists (K.N. and T.S.) according to the *DSM-IV*.[1] The subjects with ASD did not have any other psychiatric comorbidity disorders, as confirmed by applying the Structured Clinical Interview for *DSM-IV* axis I disorders.[29] In addition, they had no notable dysmorphology, 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. The Autism Diagnostic Observation Schedule (ADOS)[30] module 4 and Autism Diagnostic Interview-Revised (ADI-R)[31] were used to evaluate current and childhood autism symptoms, respectively, by trained clinicians (K.J.T. and K.M., respectively). Fifteen of 20 subjects with ASD were diagnosed with autistic disorder and remaining 5 were considered to have pervasive developmental disorder not otherwise specified according to the ADOS scores, although all 20 subjects met ADI-R criteria of autism disorder. All control subjects were found to be mentally and physically healthy according to comprehensive assessments of their medical histories and neuropsychiatric examinations. The study was approved by the local ethics committees. Written informed consent was obtained from each of the participants.

MRI AND PET PROCEDURES

As described elsewhere,[32,33] we performed 3-dimensional MRI scans using a 0.3-T MRI unit (model MRP7000AD; Hitachi Medical, Tokyo, Japan) and PET scans with a high-resolution brain PET scanner with the ability to yield 47 PET images simultaneously (model SHR-12000; Hamamatsu Photonics, Shizuoka, Japan). Details in image acquisition and preprocessing procedures are described in the online-only material (eAppendix 1; http://www.archgenpsychiatry.com). The MRI measurements and a mobile PET gantry allowed us to reconstruct PET images parallel to the anterior-posterior intercommissural line without resectioning. Using this approach, we were able to allocate a region of interest (ROI) to the target area of the PET image.[33] Before dynamic PET scanning, a 20-minute transmission scan was performed for attenuation correction using a ^{68}Ge/^{68}Ga source with the participant's head fixed by means of a radiosurgery-purpose thermoplastic face mask. Then, after a bolus intravenous injection of a 380-MBq dose of [^{11}C]MP4A, 32 serial PET scans (time frames, 4 × 30 seconds, 20 × 60 seconds, and 8 × 300 seconds) were performed for 62 minutes. No sedatives were administered during either the MRI or the PET scan.

IMAGING DATA ANALYSIS

Regional cerebrocortical AChE activities were estimated using PMOD 2.95 software (PMOD Technologies, Zurich, Switzerland). Production of parametric k_3 images was based on the reference tissue model designated for [^{11}C]MP4A k_3 value quantification,[34] and the ROI analysis was based on the reference tissue–based linear least-squares method[35] (eAppendix). In brief, a target cortical region and the cerebellum as a reference region were delineated on MRIs from each participant and transferred onto PET images. The regional k_3 value, representing the rate of tracer hydrolysis by AChE, and the R_1 value, which is the delivery of the tracer in the target region relative to the reference and reflects regional cerebral blood flow, were calculated using multilinear regression from time-activity curves from the target and reference regions.[35] The R_1 value is important for ruling out the effect of regional cerebral blood flow on the regional k_3 value. Using the PMOD, whole-brain parametric maps of k_3 and R_1 were generated. We masked extracerebral structures by demarcating cerebral regions on MRIs for further analysis of the k_3 and R_1 parametric maps.

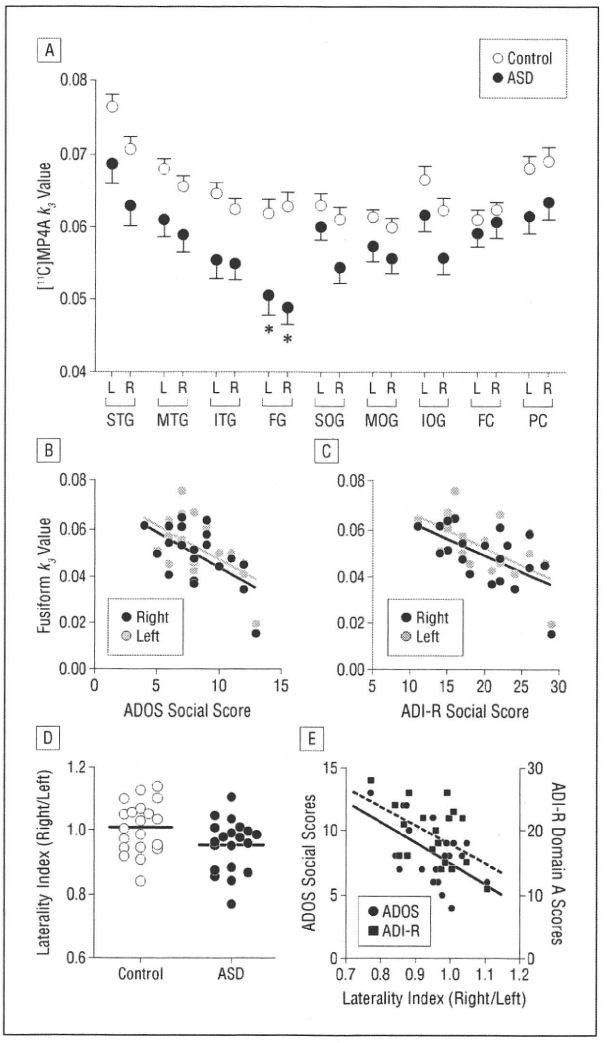

Figure 1. Results of region of interest–based analysis. A, Mean regional brain *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A) k_3 values in controls and subjects with autism spectrum disorder (ASD). Subjects with ASD had significantly lower k_3 values in the bilateral fusiform gyri compared with controls. Error bars represent the standard error of the mean. Note the significance ($P<.01$ by post hoc Bonferroni test following 2-way analysis of variance). Correlation between [^{11}C]MP4A k_3 values in the fusiform gyrus and social scores of the ADOS (B) and ADI-R (C) is shown. Values of [^{11}C]MP4A k_3 in both the right and left fusiform gyrus were significantly and negatively correlated with the Autism Diagnostic Observation Schedule (ADOS) social scores (A) as well as the Autism Diagnostic Interview–Revised (ADI-R) domain A scores (B). D, The mean laterality index (right to left ratio) of the fusiform k_3 values in controls and subjects with ASD is shown. E, Correlation between laterality index of fusiform k_3 and social scores of ADOS or ADI-R in subjects with ASD is also shown. ADI-R indicates Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; FC, dorsolateral prefrontal cortex; FG, fusiform gyrus; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PC, parietal cortex (angular gyrus); SOG, superior occipital gyrus; and STG, superior temporal gyrus.

VOXEL-BASED IMAGE ANALYSIS

We performed voxel-based whole-brain analyses using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). In the SPM analysis of [^{11}C]MP4A k_3 and R_1 parametric maps, between-group comparisons were performed to investigate regional differences in each value, using the t test for each voxel. The SPM analyses were performed without proportional scaling of k_3 and R_1 values. Correlations between k_3 and R_1 values were examined on a voxel-by-voxel basis using the Biological Parametric Mapping toolbox.[36] The Biological Parametric Mapping toolbox examines any correlation voxelwise between multimodal images that are coregistered and aligned within the same space (ie, Montréal Neurological Institute space). To test the effect of tracer delivery (R_1) on the metabolic rate (k_3), an analysis of covariance was performed using the k_3 map as the primary modality and the corresponding R_1 map as the regressor using the Biological Parametric Mapping toolbox. In addition, we performed exploratory correlation analyses between the regional changes in [^{11}C]MP4A k_3 values and the severity of social disabilities in subjects with ASD. Age and sex were treated as covariates, and the scores on the ADOS and ADIR were considered to be variables of interest. To test hypotheses about the regional specific effects of these variables, the estimates were compared using 2 linear contrasts (positive or negative correlation).

ROI-BASED ANALYSIS

In addition to the voxel-based analysis that is suitable for an exploratory examination of tracer distribution altered in the brain, we performed ROI-based analysis because it enabled us to generate quantitative differences in [^{11}C]MP4A k_3 and R_1 values in specific regions. Manual delineation on individual MRI scans in ROI-based approaches is often biased by the variability between raters and side differences in ROI size, whereby direct case-control comparability is compromised. Therefore, we chose to delineate ROIs by application of a standardized ROI template based on the Anatomical Automated Labeling atlas[37] fitting the Montréal Neurological Institute standard brain. Both the k_3 and R_1 parametric maps were normalized to the Montréal Neurological Institute space by applying a nonlinear iterative algorithm using PMOD software. Then we chose ROIs of 9 brain areas bilaterally including visual processing pathways (the fusiform gyrus, superior, middle, and inferior temporal gyri, and the superior, middle, and inferior occipital gyri), dorsolateral prefrontal cortex (Brodmann area 9), and parietal cortex (angular gyrus, Brodmann area 39). Averaged k_3 and R_1 values for each ROI were obtained. To determine whether there is laterality in the regional k_3 values, we calculated a laterality index (right k_3/left k_3) in bilateral fusiform ROIs in the 2 groups.

STATISTICAL ANALYSIS

Demographic and clinical variables were compared between the ASD and control groups using the unpaired t test using statistical software (SPSS version 17J; SPSS Japan Inc, Tokyo, Japan). In the voxel-based analyses, the results were corrected for multiple comparisons of whole-brain analysis at a significance level of $P<.05$ (false discovery rate). The significance level was determined using a voxel-level threshold of $P<.001$. In ROI-based analyses, we tested the main effect of the diagnosis of ASD on [^{11}C]MP4A k_3 or R_1 values derived from 9 brain regions using 2-way analysis of variance followed by post hoc Bonferroni test. We further conducted an analysis of covariance using the k_3 value as the independent variable and the corresponding R_1 value as the covariate in ROIs on the fusiform gyrus, based on the results of the 2-way analysis of variance (**Figure 1**A). In the laterality analysis, an unpaired t test was used for the comparison between the 2 groups. Evaluation of relationships between the regional k_3 values from each ROI and ADI-R or ADOS scores among subjects with ASD was performed with the Pearson r correlation coefficient. Statistical significance was set at $P<.05$.

RESULTS

The characteristics of all the participants are summarized in **Table 1**. There was no significant difference in the distribution of age or the sex ratio. The difference in intelligence quotient between the 2 groups did not reach statistical significance ($t=1.43$; $P=.16$). In quantitative PET brain imaging, the motion artifact is the important degrading factor. Therefore, we fixed the head of each participant using a thermoplastic face mask, observed participants carefully during each scan, and confirmed that all of the participants had remained immobilized. Another major confounding factor in PET image analysis is the partial volume effect (PVE) that can be observed in measuring small brain structures and lead to an underestimation of tracer activity. The present results were generated without PVE correction. To minimize PVE, we used a high-resolution brain-purpose PET scanner for data acquisition and MRI data for image analysis, the latter of which allowed us to select the brain loci with no extraparenchymal spaces to estimate k_3 value, an index of AChE activity, and R_1, an index of tracer delivery, with reference tissue–based linear least-squares analysis[34] of dynamic [^{11}C]MP4A PET images. When we conducted an additional volumetric brain morphometry study using a 3-T scanner on the participants of the MP4A PET study, there was no significant difference in whole-brain or regional gray matter volumes between subjects with ASD and controls (eAppendix 2, eTable, eFigure 1 and eFigure 2).

Table 1. Demographic Characteristics of the Participants

Characteristic	Mean (SD) [Range]	
	Control (n = 20)	ASD (n = 20)
Male:female, No.	14:6	14:6
Age, y	23.1 (4.2) [19-32]	23.5 (4.3) [18-33]
WAIS-III, full IQ	100.5 (19.4) [70-136]	91.6 (19.7) [70-140]
ADOS score		
Social	NA	8.6 (2.3) [5-13]
Communication	NA	4.3 (1.9) [2-8]
Stereotype	NA	0.8 (0.9) [0-3]
ADI-R score, Domain		
A (social)	NA	20.0 (5.2) [11-29]
B (communication)	NA	14.8 (5.0) [9-23]
C (stereotype)	NA	5.2 (2.3) [4-13]

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NA, not applicable; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition.

VOXEL-BASED WHOLE-BRAIN ANALYSIS

We first obtained parametric maps of k_3 and R_1 values of ASD and control subjects. **Figure 2**A illustrates normalized and averaged [^{11}C]MP4A k_3 parametric maps from control subjects and subjects with ASD. The ASD group showed significant reductions in [^{11}C]MP4A k_3 values in ventral portion of the bilateral temporal lobes compared with the control group (Figure 1B). There was no voxel where [^{11}C]MP4A k_3 values were greater in subjects with ASD than in controls. In contrast, there was no significant difference in R_1 values in the whole brain between groups (eFigure 3 and eFigure 4). Although it was found that R_1 values did not differ significantly between the ASD and control groups, to exclude further a possible adverse effect of the [^{11}C]MP4A delivery on its retention, we conducted an analysis of covariance using the k_3 map as the primary modality and the corresponding R_1 map as the regressor. After controlling the effect of R_1 value, the reduction in [^{11}C]MP4A k_3 values in the ASD group was still significant within the fusiform gyrus bilaterally (Figure 1C; $P<.05$, corrected).

We further examined the possible relationships between [^{11}C]MP4A k_3 values and clinical features in subjects with ASD (**Table 2**). Figure 1D shows a cluster on the fusiform gyrus in which the [^{11}C]MP4A k_3 values were significantly negatively correlated with the ADOS social score ($P<.05$, corrected). Figure 1E indicates a cluster on the fusiform gyrus in which a significantly negative correlation between the [^{11}C]MP4A k_3 values and the ADI-R domain A (social) score was noted ($P<.05$, corrected). Clusters associated with the ADOS social score (Figure 1D) and the ADI-R social score (Figure 1E) were located within the clusters shown in Figure 1C. The other scores in the ADOS and ADI-R did not correlate significantly with [^{11}C]MP4A k_3 values (data not shown).

ROI ANALYSIS

The results of analyses of multiple ROIs are shown in Figure 2. Consistent with the findings derived from the voxel-based analysis, [^{11}C]MP4A k_3 values in the bilateral fusiform gyri in subjects with ASD were significantly lower than the corresponding values in control subjects (Figure 2A; $t=4.91$, $P<.001$ for the right; $t=3.98$, $P=.002$ for the left). There was no difference in [^{11}C]MP4A R_1 values between subjects with ASD and controls in either side of the fusiform gyrus (eFigure 5; $t=1.47$, $P=.15$ for the right; $t=1.66$, $P=.10$ for the left). Analysis of covariance showed that differences in k_3 values between the 2 groups were significant in bilateral fusiform ROIs after controlling the effect of R_1 value ($F_{1,37}=12.51$, $P=.001$ for the right; $F_{1,37}=6.78$, $P=.01$ for the left).

Examination of the correlation between [^{11}C]MP4A k_3 values in the bilateral fusiform gyri and the clinical characteristics revealed that the [^{11}C]MP4A k_3 values were significantly negatively correlated with social scores of both the ADOS (Pearson $r=-0.559$, $P=.009$ for the right; $r=-0.512$, $P=.02$ for the left) and ADI-R ($r=-0.594$, $P=.007$ for the right; $r=-0.572$, $P=.008$ for the left) (Figure 2B for ADOS and Figure 2C for ADI-R). No correlation was found between [^{11}C]MP4A $k3$ values in the fusiform gyrus and other scores of the ADOS or the ADI-R (data not shown). Values of [^{11}C]MP4A k_3 in ROIs other than the fusiform gyrus did not correlate significantly with any ADOS or ADIR scores (data not shown).

Results from the laterality analysis of [^{11}C]MP4A k_3 values in the fusiform gyrus are shown in Figure 2, D and E. The group mean of the laterality index, a right to left ratio of the k_3 value, in subjects with ASD was significantly lower than that of controls ($t=2.21$; $P=.03$). The laterality index was weakly but significantly and negatively correlated with ADOS social scores (Pearson

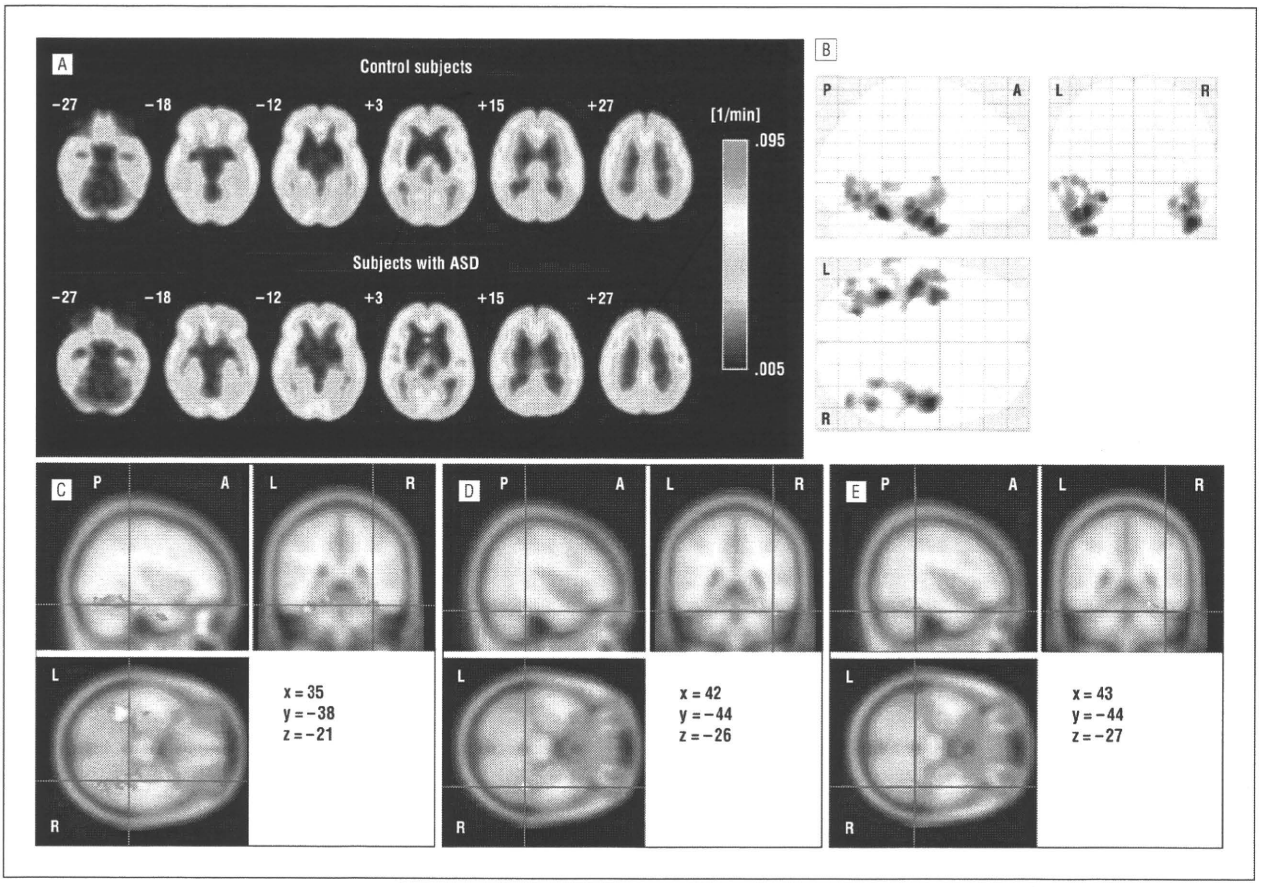

Figure 2. Results of the whole-brain voxel-based statistical parametric mapping analysis of the *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A) k_3 value distribution maps. A, Normalized and averaged [^{11}C]MP4A k_3 parametric maps from control subjects and subjects with autism spectrum disorders (ASD) are shown. B, Areas with significantly reduced [^{11}C]MP4A k_3 values in subjects with ASD compared with those in controls ($P<.05$, corrected) are rendered on glass brains. C, Results from analyses of covariance are shown. Areas with significantly lower [^{11}C]MP4A k_3 values in the ASD group than in the control group ($P<.05$, corrected) are indicated. The location of a cluster with significant negative correlations between [^{11}C]MP4A k_3 values and Autism Diagnostic Observation Schedule social scores (D) or Autism Diagnostic Interview–Revised social scores (E) in subjects with ASD ($P<.05$, corrected) is shown. The locations are rendered on the standard-brain T1 template. A indicates anterior; P, posterior;

$r=-0.508$; $P=.02$) as well as ADI-R domain A scores ($r=-0.505$; $P=.02$) (Figure 2E).

COMMENTS

Adults with ASD had significantly and locally reduced [^{11}C]MP4A k_3 values, a representative measure of the hydrolytic activity of AChE in the bilateral fusiform gyri, with no significant change in [^{11}C]MP4A k_3 values in the other cortical areas. As mentioned previously, motion during PET and PVE are potential confounding factors that influence the results of PET analysis. In this study, however, we confirmed that all of the participants had remained immobilized during each PET scan by fixing the head of each participant. An additional volumetric brain morphometry study showed no significant difference in whole-brain or regional gray matter volumes between subjects with ASD and controls (eAppendix 2, eTable, eFigure 1 and eFigure 2). Therefore, the obtained PET data may correctly represent the condition in the brain. Acetylcholinesterase is most abundant along cholinergic pathways, where it terminates neurotransmission through the rapid hydrolysis of acetylcholine. Although AChE has a very good correspondence with choline acetyltransferase, the enzyme that synthesizes acetylcholine, several other cortical AChE-rich neurons have no choline acetyltransferase activity and are classified as noncholinergic but cholinoceptive.[38,39] However, the AChE-rich cortical axons in the adult brain are almost exclusively cholinergic, arise mostly from the basal forebrain, and contain AChE that is transported anterogradely from cholinergic perikarya in the basal forebrain.[40-42] Therefore, the present result of reduction in the [^{11}C]MP4A k_3 values localized in the bilateral fusiform gyri suggests that presynaptic cholinergic innervation of a specific cortical region is selectively impaired in adult individuals with ASD. Previously, Perry et al[28] measured cholinergic enzyme activity as well as the levels of muscarinic and nicotinic receptors in the frontal and parietal cortices in deceased adults with autism and found no change in the activities of AChE and choline acetyltransferase, although there were decreases in some types of muscarinic and nicotinic receptors. The results of Perry et al[28] may support our contention that the presynaptic cholinergic innervations of the cortex, other than the restricted region of the fusiform gyrus, are intact in ASD. Serotonergic and dopaminergic, as well as cholinergic, innervations may play important roles in the regulation

Table 2. Clusters Where [^{11}C]MP4A k_3 Values Significantly Correlated With Social Scores From ADOS and ADI-R in Subjects With ASD in the Fusiform Gyrus[a]

Hemisphere	Cluster Size	*F*	x	y	z
Negatively Correlated With ADOS Social Scores					
R	58	29.92	42	−44	−26
L	16	24.92	−46	−52	−20
R	20	23.78	24	−60	−20
R	38	19.65	24	−46	−16
L	14	16.89	−28	−74	−16
Negatively Correlated With ADI-R A (Social) Scores					
R	267	32.78	38	−46	−24
L	36	28.70	−46	−52	−20
L	59	16.53	−28	−76	−16
R	39	15.55	24	−80	−16

Abbreviations: [^{11}C]MP4A, *N*-[^{11}C]methylpiperidin-4-yl acetate; ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NA, not applicable.

[a] $P<.05$, corrected; cluster extent threshold, 10 voxels.

of cortical activity in the visual area.[19] However, our recent PET study in which brain serotonin and dopamine transporter bindings were evaluated in adults with high-functioning autism showed no changes in the serotonergic or dopaminergic terminals in the fusiform gyrus.[32] Therefore, the deficit in the fusiform gyri of individuals with ASD may be relatively specific to the cholinergic neurotransmission, although more study of the influences of other neurotransmitters, such as noradrenaline, is necessary. In our ROI-based analysis, AChE activities tended to be lower in the ASD groups than in the controls across all of the ROIs tested, although it reached significance only in the bilateral fusiform gyri after correction for multiple comparisons. It may be possible that the cholinergic transmission is globally impaired in ASD. Further study is therefore required on the subject.

When the relationship between the [^{11}C]MP4A k_3 value and the diagnostic algorithm scores from the ADOS and ADI-R was examined in each side of the fusiform gyrus, lower levels of the k_3 value in both fusiform gyri were found to be associated with more severe social reciprocity, as evaluated by the ADOS and ADI-R. The ADOS social score reflects the current social function, while the ADI-R social (domain A) scoring is based on early social development. Therefore, a deficit in cholinergic innervation of the fusiform gyri, which can be observed in adults with ASD, may be related not only to the current but also the childhood impairment of social functioning. The participation of the fusiform gyrus in this regard may be more predominant in the right than the left hemisphere, since our laterality analysis showed that the individual laterality indices were negatively correlated with social scores from the ADOS and ADI-R. It is currently unknown whether children with ASD have abnormalities in cholinergic innervations of the fusiform gyri. However, a lack of interest in the human face is a major symptom of autism and is evident as early as the first year of life,[43] suggesting the emergence of a functional impairment of the face-processing system, including the FFA within the fusiform gyrus, in the early development of ASD. Although speculative, the association of the current deficit in cholinergic innervations of the fusiform gyri with the present and early impairment of social functioning may reflect the existence of the cholinergic insult in the early development of ASD, persisting into adulthood. Recently, Nacewicz et al[44] demonstrated that a smaller amygdala exhibits more significant impairment in social reciprocity as determined by the ADI-R. When Kleinhans et al,[45] using the fMRI technique, investigated functional connectivity within the limbic system during face identification in high-functioning adults with ASD, abnormal functional connectivity between the right fusiform gyrus and the left amygdala was associated with ADI-R social scores in childhood. At this time, it is unclear whether cholinergic transmission impairment in the right-hemispheric fusiform gyrus is involved in the time-independent association described by Nacewicz et al[44] and Kleinhans et al.[45]

A previous neuropathological study of autism described significant reductions in neuron density in layer III, total neuron numbers in layers III, V, and VI, and mean perikaryal volumes of neurons in layers V and VI in the fusiform gyrus.[17] The neuropathological changes may be specific to the fusiform gyrus because none of these alterations were found in the primary visual cortex or in the whole cerebral cortex.[17] The pyramidal cells in layers III and V have been suggested to be cholinoceptive.[40,46-51] Because acetylcholine is known to play an important role in the regulation of both structural and functional maturation of cortical circuits,[18,52,53] and because the modulatory effect of acetylcholine seems to depend on the level of AChE activity,[54] we suppose that the reduced AChE activity in the fusiform gyrus observed here may partly contribute to the reduction in the number of cholinoceptive neurons in layers III and V.

Our study has some limitations. The small sample size renders the data presented here preliminary, and a larger study with more ASD subjects will be necessary. However, recruitment for the current study was limited to a group of high-functioning subjects with ASD, none of whom were given psychotropic drugs, and all were able to complete PET examination without sedation. Therefore, our data are free from possible confounding factors and thus reflect a certain common pathology among