Commentary on *The Reason I Jump* by Naoki Higashida

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The Reason I Jump has received worldwide notice, and parents have asked us about the book and its implications for their own children. We have read the book in light of our experience with affected children and their families and our knowledge of the clinical and research literature. D. Fein is a child neuropsychologist and Y. Kamio is a child psychiatrist; both have specialized in autism for many years, and both have had extensive clinical and research experience with autism. The purpose of this commentary is to raise some questions about how the book was created and its significance for understanding the nature of cognitive functioning in autism. We are concerned that the book will lead parents to believe that a child with severe autism could independently create such a book and perhaps believe that every child with autism has such capability, which could be harmful to families and affected children. It is very important to us for families, physicians, psychologists, and therapists to read this book with a questioning mind and form their own opinions about the issues raised below.

Neither author of this commentary has interacted with Mr Higashida in person. Our impressions are based on the text of the book in both English and Japanese, a translated transcription of a talk Mr Higashida gave at Tokyo University in 2009, a DVD of him with his mother and a public appearance in Tokyo by him and his mother in January 2014, when he was 20 years old (attended by Y.K.).

PUBLICATION OF THE BOOK

The original version of *The Reason I Jump* was published in Japan in 2007 after the publication of several essays, poetry, and fairy tales, some of which won writing contests and for which the author was already famous. The author is Naoki Higashida, a then-13-year-old boy with autism. An English translation (by David Mitchell and K. A. Yoshida) was published in August 2013. Since then, the book has gotten a good deal of attention in the United States and abroad. It was named to the *New York Times* bestseller list, was promoted by Jon Stewart, who interviewed Mr Mitchell on The Daily Show, and was named one of the best books of the year by National Public Radio (npr.org). After the success of the translated version, Naoki and his mother received many invitations to lecture and have made public appearances. The book is a lyrical exposition about the nature of autism and the inner world of the autistic individual, with a moving introduction to the English version by Mr Mitchell and Ms Yoshida, themselves the parents of a boy with autism.

(*J Dev Behav Pediatr* 35:539–542, 2014) **Index terms:** autism, book, autobiography.

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WHO IS RESPONSIBLE FOR THE IDEAS IN THE BOOK?

The question that naturally arises for the reader is the extent to which Naoki generated the ideas in the book. If he created the content independently, this would indeed be inspiring and comforting to other individuals with autism and to their families. The hope of an outcome like that apparently achieved by Naoki, that of an expressive and successful writer, may be uplifting to those who love, care for, and teach children with autism. But if he is not the independent creator of the content, then the situation is quite different.

First is the question of the translation. One of us (Y.K.) was able to read both the English and Japanese versions. The English translation eliminates some redundancies in the Japanese and is a bit more concise but is generally an accurate translation. That leaves the question of how much of the original text was created by Naoki.

Although it is impossible to answer this question with certainty, there is sufficient reason to doubt that Naoki is in fact the independent creator of the book's eloquent prose.

The voice of the author does not seem to us to be that of a 13-year-old, let alone that of a young man with autism and limited verbal skills. We could cite much of the book as examples of that, but here are a few quotes to illustrate: The answer to why he jumps is (from the English translation): "...the motion makes me want to change into a bird and fly off to some faraway place. But constrained by ourselves and by the people around us, all we can do is tweet-tweet, flap our wings and hop around in a cage." "So *why* can't I do these things? During my frustrating, miserable, helpless days, I've started imagining what it would be like if everyone was autistic. If autism was regarded simply as a personality type, things would be so much easier and happier for us than they are now. For sure, there are bad times when we cause a lot of hassle for other people, but what we really want is to be able to look toward a brighter future." In answer

to "Why do you like being in the water?" he writes, "We just want to go back. To the distant, distant past. To a primeval era, in fact, before human beings even existed. All people with autism feel the same about this one, I reckon. Aquatic life-forms came into being and evolved, but why did they then have to emerge onto dry land, and turn into human beings who chose to lead lives ruled by time? These are real mysteries to me." In answer to "Why can't you have a proper conversation", Naoki writes, "For a long time, I've been wondering why us, people with autism, can't talk properly. I can never say what I really want to. Instead, verbal junk that hasn't got anything to do with anything comes pouring out of my mouth. This used to get me down badly, and I couldn't help envying all those people who speak without even trying. Our feelings are the same as everyone else's, but we can't find a way to express them."

In a lecture in May 2009 at Tokyo University, he said, similarly, "...I always had had words inside of me much like everyone else even before I started to write with support. During that time, I waited for someone who could rescue the real me out of my body that was like a broken robot..." (English translation can be seen at http://katari.umin.jp/report_20090523/report_naoki_en.html.). Naoki's official blog in Japanese is at http://higashida999.blog77.fc2.com/blog-entry-741.html.

The sophistication of the thinking and knowledge behind these quotes, we feel, has to raise questions about how independently they could be produced by a 13-year-old, especially one with the degree of autism that Naoki appears to have.

DISSOCIATION OF WRITING FROM SPEAKING

The premise of the book and lecture, as the above quotations make clear, is that the internal life of people with autism is like that of same aged peers with typical development, but that overwhelming sensory input or difficulty speaking causes them to have trouble in concentrating and communicating, destructive or odd behavior, and the appearance of cognitive limitations. However, with sufficient practice, the ability to write is left unimpaired.

The dissociation that Naoki claims to have of observable behavior from mental life, that what can be observed in language and behavior is not indicative of the individual's thoughts and feelings, does exist in some cases of neurological dysfunction. Locked-in syndrome is the most obvious case in which sometimes normal cognition is not able to be expressed except through very limited voluntary movement, such as eye movement. Dissociation of speaking from writing in which individuals can express themselves in writing but not in speech is seen in aphemia, a relatively rare condition of severe dysarthria in which anterior language areas lose their connection with motor speech areas but not with writing output centers, resulting in severely impaired articulation but unimpaired writing.[1] However, when Naoki does speak, although the content is limited, his articulation and fluency are almost unimpaired, making it very unlikely that he suffers from this language-motor dissociation.

IS THIS A FORM OF FACILITATED COMMUNICATION?

The process by which Naoki communicates is strikingly reminiscent of "facilitated communication," a process in which a "facilitator" helps the autistic individual with more or less direct physical support to type messages that he or she is unable to speak. In many cases, the gap between the sophistication of the typed messages and the much more limited cognitive level of the individual as ascertained through multiple other means, immediately calls into question the affected individual as the actual source. Facilitated communication has been quite thoroughly investigated (see reviews by Jacobson et al[2]; Mostert[3]; Simpson and Myles[4]). In virtually every case in which the facilitator was blind to the questions posed to the individual, the individual was unable to answer the questions independently. The assistance given by the facilitator is probably unconscious in many cases. As a result of these and other controlled studies, facilitated communication has been declared to lack reliability or validity by multiple organizations, including the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry, and the American Psychological Association, among others.

Naoki calls his current writing system "facilitated finger writing" (in the translation of his 2009 talk at Tokyo University) and then describes how he gradually reduced the amount of physical support he needed from hand-over-hand to support on the elbow, shoulder, then back, and finally independent typing. In a video of his communication from around the time *The Reason I Jump* was written, Naoki is seen sitting with his mother. Although we cannot say that he is always in physical contact with his mother, in this video, she appears to have a hand on his back, shoulder, or leg most of the time. It is possible that he is receiving physical cues from her about what to type or that he is typing independently, perhaps typing previously memorized text and that her physical prompts are to keep him engaged in this activity. In his 2014 public appearance, Naoki answered questions (through typing and simultaneously speaking aloud) with what seemed like previously memorized, general answers, such as "why do you ask me? I think this. But everyone has an answer. You should ask your child." The way he spoke made him difficult to understand because he appeared to take an equal amount of time for each phrase regardless of its length, in addition to having an atypical prosody.

Some commentaries on this book suggest that Naoki is nonverbal, which is not true (*The UK Sunday Times*, July 14, 2013 and *The New York Times*, review August 23, 2013). In the public appearance and in the DVD,

he does speak, with the unusual prosody just mentioned, and what sounds like repetitive and echolalic speech, sounding quite like many children with autism we have both seen. He shows facial grimacing and atypical vocalizing as well. Naoki clearly does some typing independently, looking intently back and forth between the keyboard and the screen but there is nothing to indicate that what he produces is something other than the memorized sequences of characters, which he then reads aloud. In one scene of the DVD, he copies a flower and prints English words (e.g., aquarium), so he clearly has good motor control, printing and copying the flower quite neatly, and this again is typical of many autistic children we have seen (having good fine motor control and favorite words or pictures to write again and again). The good vocal and manual motor control he displays again calls into question the assumed dissociation between mental life and motor output that underlies claims of validity for facilitated communication.

WHY QUESTION THE AUTHORSHIP OF THIS BOOK?

Why is it necessary to raise the question of who created the prose in this book? What harm is done by leaving unchallenged the supposition that the named author is the actual creator of this content? It is not our intention to question the sincerity of anyone involved in the production of this book. Both of us know many families with children with autism, and we understand how much pain a family can feel when confronted with the reality of significant disability. Disappointment and anger at researchers, clinicians, and agencies who have failed them and their children are manifested in the words of the translators and of Naoki's mother. Many families feel the same way. A book like this may be viewed as a testament to the fact that autism as a disability is less severe and more circumscribed than appears, and that normal, even sophisticated thinking and feeling may be present in these children without a way to be expressed. So, what is the problem with just accepting the book at face value?

First, we are very concerned that promoting this book to parents of children with autism as coming from a "typical" autistic child, who is claiming to have deep insight into his condition and to speak for other autistic individuals, will cause parents to feel unwarranted guilt when they are unable to unlock those insights in their own children.

Second, the book may also lead parents of children with significant cognitive or language limitations to expect that their child will be capable of producing such work. Of course, all children should be encouraged and helped to fulfill their cognitive potential and their ability for self-expression. In our opinion, no limits should be placed on the potential of young children who have not yet received effective intensive intervention because prediction of outcome is extremely uncertain at this point. However, after a number of years of good intervention, it is generally possible to have some idea of likely cognitive and functional outcome; at this time, assessment of cognitive function can be valid and stable and consistent across multiple methods of testing. Such assessment can help families determine realistic goals for their child.

Third, the book may sway parents' goals and their teaching methods in ways that do not benefit the child or, ultimately, the family. The goals for all children should be to help them make real progress in cognition, communication, social interaction, and self-help skills. We frequently see children with limited ability to communicate. What they need is verbal, gestural, or picture methods to communicate what they feel and what they need, with the communication truly coming from them. We are not advocating limited goals for children with autism. In fact, we have both done research on children with autism who progress to fully typical cognitive and language functioning and a loss of diagnosis. Rather, we are advocating realistic goals and effective interventions. Although *The Reason I Jump* does not advocate any specific interventions, a parent could easily take away the message that the child should be accepted as he/she is, without trying to implement behavioral plans or structured teaching, methods that have the most evidence-based promise for promoting real progress.

Finally, if the content of Naoki's book was indeed created independently by this child, then most of our ideas about autism, arising from 40 or more years of intensive research, are incorrect. Of course, challenges to the body of research must always be entertained seriously. However, if one is going to invalidate 40 years of carefully accrued and internally consistent results about language, cognition, and communication in moderate-to-severe autism, one would like some assurance that the challenge comes from a valid source. The claim that a young man as affected as Naoki obviously is by autism can produce the sophisticated prose in this book is an extraordinary one, and as Carl Sagan put it, extraordinary claims require extraordinary evidence.

HOW COULD SUCH EVIDENCE BE PROVIDED?

It would be extremely easy to provide assurance that Naoki has the capacity to write prose of this level of sophistication. One could simply provide some written or verbal material to him alone and not to the adults who care for him and then test his comprehension of it by any means suggested. For example, he could write answers to questions or even simply answer yes/no questions about the material by writing, speaking, or pointing to yes or no; or a question could be put to Naoki and not made accessible to others, and then his ability to answer it by any independent means could be tested, as has been done repeatedly with facilitated communication.

We want to also explicitly make the point that we highly value first-person accounts of autism experience,

when the independent authorship is beyond question. Accounts such as those of Temple Grandin, John Elder Robison, Stephen Shore, Tim Page, and in Japan, Naomi Moriguchi and Rinko Niki, and many others, are full of valuable insights about all aspects of lifespan experience and have generated productive research ideas, clinical strategies, and social support networks. In these cases, however, the productions of these authors are consistent with the entirety of their functioning, and there is no doubt about the independence of their authorship. For interested readers, additional first-person accounts are listed on the Asperger's syndrome and High-Functioning Autism website (ahany.org) and a special issue (*Winter, 2000*) of *Focus on Autism and Other Developmental Disabilities* is devoted to first-person accounts.

WHAT IS OUR MESSAGE FOR FAMILIES?

What will we tell parents who ask us about this book? Simply, the level of writing in the book does not appear to us to be consistent with the thinking of a 13-year-old child, with autism or not. Difficult as it may be, facing the true levels of functioning of any child should be the basis for planning interventions. That is the only way to help the child make real progress and to assess such progress. Severe autism is not simply a motor or expressive language disability in which normal mental life is prevented from finding expression but a complex disability affecting thinking, emotion, behavior, and language and in which each child has his or her own profile of ability and impairment. It is quite possible to validly assess a child's approximate level of vocabulary, knowledge, and reasoning, making whatever adaptations are necessary to standardized tests (as we frequently do) to best demonstrate the child's current level of functioning.

In questioning the source of the book's material, it is not our intention to discount the pain, effort, and devotion of families or the respect that individuals with autism deserve for their own pain, their struggles, and their hard work. But along with respect, children with autism and their families deserve honest and scientific scrutiny of claims and have a right to individualized, evidence-based services. Only then, can we advocate effectively for the understanding and interventions that can bring about real improvements in the lives of young people with autism.

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Autistic empathy toward autistic others

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Individuals with autism spectrum disorder (ASD) are thought to lack self-awareness and to experience difficulty empathizing with others. Although these deficits have been demonstrated in previous studies, most of the target stimuli were constructed for typically developing (TD) individuals. We employed judgment tasks capable of indexing self-relevant processing in individuals with and without ASD. Fourteen Japanese men and 1 Japanese women with high-functioning ASD (17–41 years of age) and 13 Japanese men and 2 TD Japanese women (22–40 years of age), all of whom were matched for age and full and verbal intelligence quotient scores with the ASD participants, were enrolled in this study. The results demonstrated that the ventromedial prefrontal cortex was significantly activated in individuals with ASD in response to autistic characters and in TD individuals in response to non-autistic characters. Although the frontal–posterior network between the ventromedial prefrontal cortex and superior temporal gyrus participated in the processing of non-autistic characters in TD individuals, an alternative network was involved when individuals with ASD processed autistic characters. This suggests an atypical form of empathy in individuals with ASD toward others with ASD.

Keywords: autism spectrum disorder; empathy; self; similarity; ventromedial prefrontal cortex

INTRODUCTION

As suggested by the term 'autism', which comes from the Greek word autós, meaning self, a lack of self-awareness is a central element of autism spectrum disorder (ASD) (Toichi *et al.*, 2002; Lombardo *et al.*, 2010). Deficits in self-related processing lead to difficulties in empathizing with others (Lombardo *et al.*, 2007). Individuals with ASD also show deficits in reciprocal social interactions and impairment in verbal communication, such as difficulties in understanding humor, irony and sarcasm (Frith, 2003). These pragmatic language impairments are thought to be based on deficits in theory of mind, the ability to attribute mental states to oneself and to others. This ability to make inferences about what other people think allows one to predict their behaviors (Baron-Cohen *et al.*, 1985). During the process involved in making inferences, the theory of mind network, including the medial prefrontal cortex, precuneus (and posterior cingulate cortex) and temporoparietal junction (and adjunct superior temporal sulcus), is recruited when individuals reflect on themselves and others (Amodio and Frith, 2006; Frith and Frith, 2006; Mitchell *et al.*, 2006a,b; Saxe *et al.*, 2006; Lombardo *et al.*, 2010). Several brain imaging studies have investigated the neural basis of theory of mind in TD individuals (Fletcher *et al.*, 1995; Baron-Cohen *et al.*, 1999; Castelli *et al.*, 2000; Gallagher *et al.*, 2000, 2002; Vogeley *et al.*, 2001; Ferstl and von Cramon, 2002). The theory of mind network is altered in ASD (Mason *et al.*, 2008; Mizuno *et al.*, 2011; Morita *et al.*, 2012).

Observations in ASD groups lacking theory of mind and/or empathy as well as recent neuroimaging research have provided empirical evidence of a neural basis for theory of mind and empathy (Völlm *et al.*, 2006; Bird *et al.*, 2010). Impairment in theory of mind has been implicated in neurodevelopmental disorders in ASD (Lombardo *et al.*, 2007). Additionally, previous studies on brain connectivity have demonstrated that the degree of synchronization in activation (i.e. functional connectivity) between frontal and posterior brain regions is lower in ASD. The first report of this nature was in the context of a language comprehension task (Just *et al.*, 2004); undersynchronization of activation during cognitive tasks has been reported between the frontal lobe and more posterior regions in several other paradigms (Just *et al.*, 2004, 2012; Kana *et al.*, 2006, 2009).

Although deficits in ASD have been demonstrated in previous studies, most of the target stimuli used in those studies were constructed for typically developing (TD) individuals. However, it may be difficult for individuals with ASD to understand TD individuals, just as it is difficult for TD individuals to understand those with ASD. Concerning the similarity between self and other brain regions, ventral parts of the medial prefrontal cortex (mPFC) respond both during self-referential processing (Kelley *et al.*, 2002; Northoff *et al.*, 2006) and during mental

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state inferences concerned with others (Gallagher *et al.*, 2000, 2002; Frith and Frith, 2006). The neural substrates underlying self-referential thought and theory of mind are characterized by overlap (Mitchell *et al.*, 2005, 2006b; Jenkins *et al.*, 2008; Tamir and Mitchell, 2010).

Previous studies demonstrated a lack of preferential responsiveness to self-information in the ventromedial prefrontal cortex (vmPFC) in individuals with ASD (Lombardo *et al.*, 2010; Pfeifer *et al.*, 2013). Compared with those with ASD, TD individuals recruited the vmPFC to a significantly greater extent for self *vs.* other in the reflective mentalizing task and in tasks pertaining to physical self-judgments and the British Queen. Previous behavioral studies have demonstrated that individuals with ASD do not benefit from self-referential elaboration (Toichi *et al.*, 2002; Lombardo *et al.*, 2007) and display a lack of 'neural self-reference effect' in the vmPFC (Lombardo *et al.*, 2010).

When readers and characters are matched in personality, TD readers empathize with story characters similar to themselves (Komeda *et al.*, 2013b). If this were also the case for individuals with ASD, these individuals may show empathy, a process in which one identifies with similar others. Additionally, the self-related brain network of individuals with ASD may participate in interactions with targets who have autistic traits. We used self- and other judgment tasks to test these hypotheses (Figure 1). Participants read sentences and responded to questions about them using two buttons (Yes and No). On the basis of the items in the Social Responsiveness Scale (SRS; Constantino and Todd, 2005; Kamio *et al.*, 2009, 2013), each sentence described the behavior of a target character with traits identified as autistic or non-autistic. For example, self-judgments and other judgments about autistic and non-autistic characters involved participants' reading a description about a character (e.g. 'I would rather be alone than with others' and 'Yuya would rather be with others than be alone', respectively) and evaluating their identification with this description (i.e. 'Do you agree with the sentence?' and 'Do you think you are similar to him?'). Sex was matched between participant and character.

We predicted that similarities between perceivers and targets would facilitate empathy, leading to selective responses toward targets similar to themselves. This prediction is known as the similarity hypothesis (Komeda *et al.*, 2013a,b). Recent studies on TD adults have demonstrated that similarities between readers and characters play a critical role in cognitive tasks such as story comprehension and memory. For example, personality is an important contributor to similarities between readers and characters (Komeda *et al.*, 2009, 2013b). Indeed, it is easier for highly extraverted than for less extraverted participants to understand stories about a highly extraverted story character (Komeda *et al.*, 2009). Additionally, highly extraverted readers judge the behavioral outcomes of highly extraverted fictional characters more rapidly than do less extraverted readers, and highly neurotic readers judge the outcomes of highly neurotic characters more rapidly than do less neurotic readers (Komeda *et al.*, 2013b).

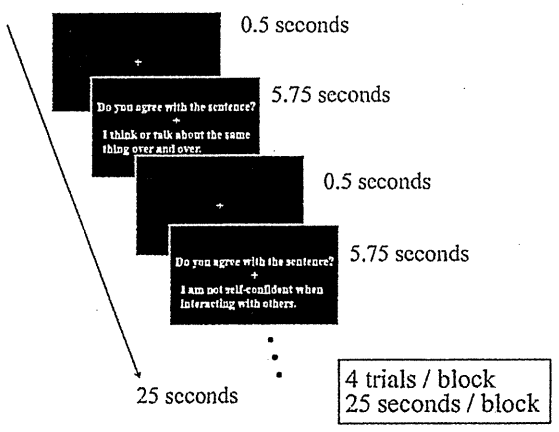

Fig. 1 We employed a block design for the experiment. Schematic depiction of stimuli and task design of each block in the fMRI study. First, a fixation crosshair was presented, followed by the experimental stimuli, which were displayed for 5.75 s. The top line in each stimulus-containing rectangle presented a question ('Do you agree with the sentence?' for a self-task and 'Do you think you are similar to him/her for an other task'), and the bottom line described a response with or without autistic traits.

Individuals with ASD provide specific responses to autistic fictional characters (Komeda *et al.*, 2013a). For example, in the case of episodes about ASD characters, individuals with ASD more effectively retrieved consistent outcomes than inconsistent outcomes, and TD individuals retrieved stories with TD characters more effectively than stories with autistic characters. Thus, similarity between reader and fictional character had different effects on the memory retrieval of individuals with and without ASD.

In this study, we used functional magnetic resonance imaging (fMRI) to investigate whether activation of the vmPFC, known to be involved in self-related information processing (Lombardo *et al.*, 2007; Tamir and Mitchell, 2010; Pfeifer *et al.*, 2013) and empathy (Shamay-Tsoory *et al.*, 2009; Schulte-Rüther *et al.*, 2011; Shamay-Tsoory, 2011), was observed when participants made judgments about characters similar to themselves. We also examined whether seed-to-voxel functional connectivity differed among groups.

METHODS

Participants

Fourteen Japanese men and 1 Japanese women with high-functioning ASD (between 17 and 41 years of age) were recruited at the Department of Neuropsychiatry of the University of Fukui Hospital, Japan, and the Department of Psychiatry and Neurobiology of the Kanazawa University Hospital, Japan. Psychiatrists (i.e. H.K. and T.M.) diagnosed participants based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) and on the standardized criteria of the Diagnostic Interview for Social and Communication Disorders (Wing *et al.*, 2002), which reportedly possesses good psychometric properties (Nygren *et al.*, 2009). This instrument also contains items on early development and a section on activities of daily living, which provide data about functioning in areas other than social and communication-related domains (Wing *et al.*, 2002). The ASD group consisted of 12 participants with autistic disorder and 3 with Asperger's disorder. Thirteen TD Japanese men and two TD Japanese women (between 22 and 40 years of age), matched for age and full and verbal intelligence quotient (IQ) scores, were recruited from the local community (Table 1). Participants were excluded if they had a history of major medical or neurological illness, including epilepsy or significant head trauma, or a lifetime history of alcohol or drug dependence. Participants with a first-degree relative with a DSM-IV Axis I disorder were also excluded. IQ assessments were performed using the Wechsler Adult Intelligence Scale III (Wechsler, 1997). All participants had full-scale IQ scores >85. Although there was a significant difference in performance IQ scores[1] between the ASD and the TD groups, there were no significant group differences for age or full-scale and verbal IQs ($P > 0.05$). To quantify autistic traits, we used the Autism-Spectrum Quotient (AQ) (Baron-Cohen *et al.*, 2001), which consists of the following five subscales: social skills, attention switching, attention to detail, communication and imagination.

[1] Effects on performance IQ were not controlled in the subsequent analyses, as we found no significant correlation between performance IQs and parameter estimates for ROIs, including the vmPFC ($r = -.27$, $P > 0.05$).

Table 1 Mean chronological age, full-scale IQ, verbal IQ, performance IQ and AQ scores in individuals with ASD and TD adults

	ASD group ($n=15$)	TD group ($n=15$)	T	P
Age (years)	26.7 (5.8)	26.1 (5.2)	−0.30	0.77
Full-scale IQ	99.7 (12.0)	107.4 (9.8)	−1.9	0.06
Verbal IQ	104.6 (14.8)	108.5 (10.8)	−0.82	0.42
Performance IQ	92.1 (16.1)	104.3 (8.3)	−2.6*	0.01
AQ	32.0 (8.5)	14.6 (5.5)	6.6*	0.00

Note: Data are expressed as mean (s.d.).
*$P<.05$.

The protocol used for this study was approved by the ethics committee of the University of Fukui. After a complete explanation of the study, all the participants gave written informed consent prior to participation.

Stimuli

Each sentence described the behavior of a target character with autistic or non-autistic traits, as determined using the SRS (Figure 1). The use of the Japanese version of the SRS was permitted by Western Psychological Services. Making self-judgments involving an autistic character involved reading a sentence (e.g. 'I would rather be alone than with others') and answering the following question: 'Do you agree with the sentence?' Making other judgments involving a non-autistic character involved reading a sentence [e.g. 'Yuya (Japanese male name) would rather be with others than alone'] and answering a different question: 'Do you think you are similar to him?' The subject of the sentence was 'I' in the self-judgment task, whereas the subject was the name of a Japanese character in the other judgment task. Four experimental conditions were used: autistic character in self-judgments, autistic character in other judgments, non-autistic character in self-judgments and non-autistic character in other judgments. Sex was matched between the participant and the character.

Experimental procedure

During the fMRI scan, participants read the sentences and made judgments about them by pressing a button with the right index (for Yes responses) or middle finger (for No responses). In each trial (5.75 s), subjects were presented with a self-judgment ('Do you agree with the sentence?') or an other judgment ('Do you think you are similar to him/her') in the top line, followed by a sentence describing a character with or without autistic traits in the bottom line (Figure 1).

We used a block design, which was the most efficient means of detecting activation (Friston *et al.*, 1999; Handwerker *et al.*, 2004; Meltzer *et al.*, 2008). During scanning, the subjects performed a total of 6 sessions (each lasting 4 min 22.5 s, with 10 blocks for each of the 5 conditions, including fixation rest blocks). Eight trials were conducted under each experimental condition (autistic character in self, autistic character in other, non-autistic character in self and non-autistic character in other judgment), and each sessions included 32 experimental trials. A total of 6 sessions (192 experimental trials) were conducted, yielding 48 trials for each experimental condition (192 trials/4 conditions). Within each session, the blocks were ordered differently, and the order of the six sessions was counterbalanced across subjects.

Imaging parameters

Functional images were acquired with T2*-weighted gradient-echo echo-planar imaging (EPI) sequences with a 3-T MR imager (Signa Excite; General Electric Medical Systems, Milwaukee, WI) and a standard birdcage head coil. There were 6 fMRI runs; during each run, 105 volumes were acquired. Each volume consisted of 40 slices with a thickness of 3 mm and a 0.5 mm gap to cover the entire brain. The time interval between two successive acquisitions of the same slice (TR: Repetition time) was 2500 ms, with an echo time (TE: Echo time) of 25 ms and a flip angle (FA) of 80°. The field of view was 192 × 192 mm and the matrix size was 64 × 64, giving voxel dimensions of 3 × 3 mm. Three-dimensional, inversion recovery-prepared spoiled gradient echo images (TR = 7.12 ms, TE = 3.06 ms, FA = 8°, matrix size = 256 × 256, slice thickness = 1 mm; in total, 166 transaxial images) were obtained as a high-resolution anatomical reference for each subject.

Imaging processing and statistical analysis

The first 5 volumes of each fMRI session were discarded because of unsteady magnetization, and the remaining 100 volumes per session were used for analysis. Image and statistical analyses were performed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab R2014a (Mathworks, Sherborn, MA). The images were realigned to correct for dislocations caused by head motion. The realigned images were normalized to the Montreal Neurological Institute (MNI) atlas (Shorvon *et al.*, 1994). Finally, the anatomically normalized fMRI images were filtered using a Gaussian kernel with a full width at half-maximum of 8 mm in the x, y and z axes.

Functional connectivity analyses are affected by the head motion of participants during fMRI scanning (Müller *et al.*, 2011; Power *et al.*, 2012; Jung *et al.*, 2014; Tyszka *et al.*, 2014). To assess the effects of head motion and motion artefacts during functional connectivity analyses, the root mean square of six movement parameters obtained during the realignment process (x, y, z translations and x, y, z rotations), mean frame-to-frame root mean square motion (Van Dijk *et al.*, 2012) and frame-wise displacement (FD) (Power *et al.*, 2012) were calculated for each participant. There were no significant group differences in mean frame-to-frame root mean square motion ($P>0.05$) or FD ($P>0.05$).

After preprocessing, task-related activation was evaluated with the general linear model (Friston *et al.*, 1995; Worsley and Friston, 1995). The design matrix for the single-subject analyses contained four task-related regressors (self-judgments for an autistic character, other judgments for an autistic character, self-judgments for a non-autistic character and other judgments for a non-autistic character). Regressors of interest (condition effects) were generated using a boxcar function, convolved with a hemodynamic response function. Regressors that were of no interest, such as the session effect and high-pass filtering (128 s), were also included to eliminate the low-frequency trend. To exclude the effects of head motion, motion regressors were included in single-subject models. Motion regressors based on realignment estimates were included as nuisance regressors during general linear model estimation.

In the second-level analysis, a three-way analysis of variance (ANOVA) with group (ASD or TD) as a between-subject factor and character (autistic or non-autistic) and judgment (self or other) as within-subject factors was performed for the mean response using the contrast images specified above. The analyses searched for brain regions showing a significant interaction between group and character. We employed a statistical threshold of $P<0.001$ and a spatial extent of at least 10 voxels for these whole-brain analyses. Next, a correlation analysis was performed with the individual psychological measurements. We identified regions of interest (ROIs) as spheres with 12 mm radii centered on the maximal foci of activation, using an interaction contrast between group and character for the whole-brain analyses, and extracted the volume of images. We assessed the correlation between autistic traits (AQ scores) and ROIs as follows:

correlations involving the vmPFC were based on the interaction between group and character.

Finally, we conducted functional connectivity analyses by a seed-driven approach with the 'Conn toolbox' software (Whitfield-Gabrieli and Nieto-Castanon, 2012). The toolbox removes confounding effects related to white matter or cerebrospinal fluid signal as well as motion parameters. It analyses the connectivity between one or multiple seed areas and the whole brain. We defined the vmPFC as a seed (the coordinates (4, 48, −8) in MNI space). This location was defined by brain activation results based on the interaction between group and character in self- and other judgments. The main area of interest in connectivity analyses was the network between the vmPFC (4, 48, −8) and other brain areas.

RESULTS

Behavioral results

We conducted a three-way ANOVA based on the number of 'Yes' responses with group (ASD or TD) as a between-subjects factor and character type (autistic or non-autistic) and judgments (self or other) as within-subject factors (Figure 2, Table 2). The behavioral results revealed a significant interaction between group and character ($F(1, 28) = 23.58$, $P < 0.05$, MS_e (mean squared error) $= 265.02$, $Prep = 0.99$, $\eta_p^2 = 0.46$). *Post hoc* analyses showed that the ASD group gave Yes responses for autistic characters more than the TD group did ($F(1, 28) = 14.60$, $P < 0.05$, $MS_e = 185.40$, $Prep = 0.99$, $\eta_p^2 = 0.34$), whereas the TD group gave Yes responses for non-autistic characters more than the ASD participants did ($F(1, 28) = 29.76$, $P < 0.05$, $MS_e = 120.05$, $Prep = 0.99$, $\eta_p^2 = 0.52$).

The ASD group showed no significant difference in the frequency of Yes responses for autistic characters *vs.* non-autistic characters ($F(1, 14) = 0.12$, $P > 0.05$, $MS_e = 364.17$, $Prep = 0.60$, $\eta_p^2 = 0.01$), whereas the TD group gave Yes responses more frequently for non-autistic characters than for autistic characters ($F(1, 14) = 66.58$, $P < 0.05$, $MS_e = 165.87$, $Prep = 0.99$, $\eta_p^2 = 0.83$).

We conducted a three-way ANOVA based on reaction times with group (ASD or TD) as a between-subjects factor and character type (autistic or non-autistic) and judgments (self or other) as within-subject factors (Table 2). The main effect of group was not significant ($F(1, 28) = 1.67$, $P > 0.05$, $MS_e = 1\,498\,512.22$, $Prep = 0.81$, $\eta_p^2 = 0.06$). The three-way interaction ($F(1, 28) = 0.76$, $P > 0.05$, $MS_e = 17\,738.61$, $Prep = 0.73$, $\eta_p^2 = 0.03$), the two-way interaction between group and character ($F(1, 28) = 1.44$, $P > 0.05$, $MS_e = 19\,355.85$, $Prep = 0.80$, $\eta_p^2 = 0.05$) and the two-way interaction between group and judgment ($F(1, 28) = 0.15$, $P > 0.05$, $MS_e = 21\,739.98$, $Prep = 0.61$, $\eta_p^2 = 0.01$) were not significant. However, the interaction between character and judgment was significant ($F(1, 28) = 5.16$, $P < 0.05$, $MS_e = 17\,738.61$, $Prep = 0.94$, $\eta_p^2 = 0.16$). *Post hoc* analyses showed that self-judgments for autistic characters were faster than self-judgments for non-autistic characters ($F(1, 28) = 11.19$, $P < 0.05$, $MS_e = 12\,650.43$, $Prep = 0.98$, $\eta_p^2 = 0.29$), and the other judgments for autistic characters were faster than other judgments for non-autistic characters ($F(1, 28) = 26.44$, $P < 0.05$, $MS_e = 24\,444.03$, $Prep = 0.99$, $\eta_p^2 = 0.49$). *Post hoc* analyses also showed that self-judgments were faster than other judgments for both autistic ($F(1, 28) = 26.88$, $P < 0.05$, $MS_e = 20\,373.67$, $Prep = 0.99$, $\eta_p^2 = 0.49$) and non-autistic ($F(1, 28) = 71.38$, $P < 0.05$, $MS_e = 19\,104.91$, $Prep = 0.99$, $\eta_p^2 = 0.72$) characters.

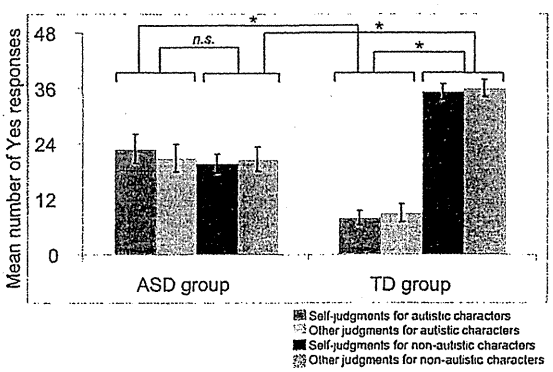

Fig. 2 Behavioral results for self- and other judgments. The number of Yes responses is shown in ASD and TD groups. Because 48 trials were conducted under each condition, scores ranged between 0 and 48. Dark orange bars denote self-judgments for autistic characters; light orange bars denote other judgments for autistic characters; dark blue bars denote self-judgments for non-autistic characters; and light blue bars denote other judgments for non-autistic characters. Error bars indicate standard errors. *$P < 0.05$.

Brain activation results

We investigated the brain activation associated with the interaction between group and character (Table 3). Results were thresholded at $P < 0.001$ (uncorrected) for a spatial extent of at least 10 voxels. The inferior frontal gyrus (IFG), postcentral gyrus, paracentral lobule, precuneus, cuneus, lingual gyrus, cerebellum, fusiform and superior frontal gyrus and vmPFC were activated in both groups when the ASD group judged characters with and the TD group judged characters

Table 2 fMRI rating and reaction-time data

	Number of Yes responses		Reaction times (ms)	
	ASD group	TD group	ASD group	TD group
Self-judgments for autistic characters	22.9 (12.2)	7.9 (6.0)	3607.7 (501.9)	3338.3 (709.1)
Other judgments for autistic characters	20.9 (11.7)	9.0 (7.6)	3788.0 (585.2)	3540.1 (677.1)
Self-judgments for non-autistic characters	19.7 (8.0)	35.2 (6.6)	3714.1 (461.4)	3426.1 (715.3)
Other judgments for non-autistic characters	20.6 (10.5)	35.9 (7.2)	4047.2 (576.4)	3696.1 (708.8)

Note: Data are expressed as mean (s.d.).

Table 3 Contrast tables and regions of activation for the interaction between group and character

Region	BA	Cluster size	*T*	MNI coordinates		
				x	*y*	*z*
IFG	47	38	3.95	−26	26	−20
Postcentral gyrus	5	61	3.78	−6	−50	74
Paracentral lobule	4	61	3.30	−6	−40	76
Precuneus	7	61	3.25	−8	−66	64
Cuneus	18	14	3.56	4	−100	10
Lingual gyrus	18	80	3.54	14	−82	−16
Cerebellum		80	3.52	20	−76	−20
Fusiform gyrus	37	18	3.47	48	−54	−22
Paracentral lobule	6	11	3.41	2	−34	76
SFG	6	14	3.41	0	−2	74
vmPFC	10	10	3.39	4	48	−8

BA = Brodmann area; SFG = superior frontal gyrus.
Self ASD = self-judgments for autistic characters; other ASD = other judgments for autistic characters; self non-ASD = self-judgments for non-autistic characters; other non-ASD = other judgments for non-autistic characters.
$P < 0.001$, uncorrected at the voxel level for a spatial extent of at least 10 voxels.

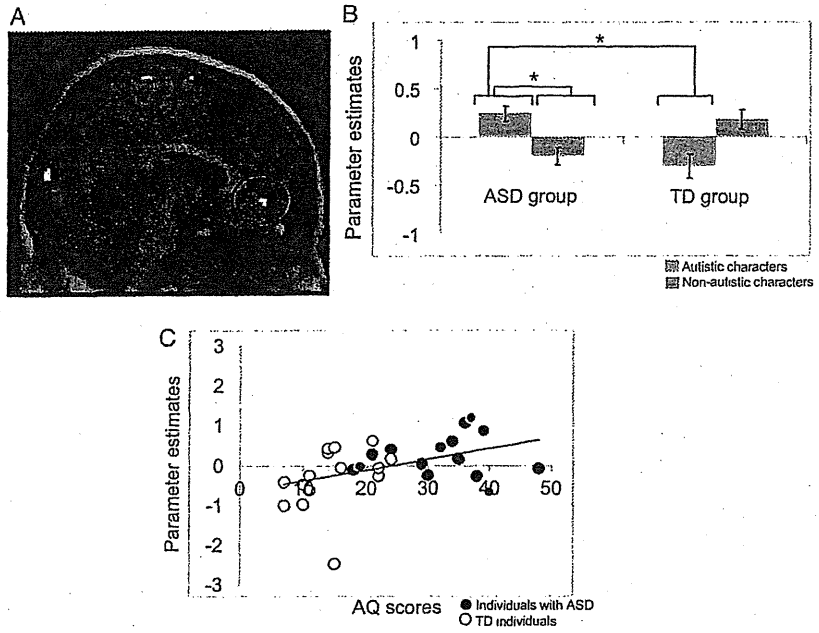

Fig. 3 (A) Brain activation in self- and other judgments. $P < 0.001$, uncorrected at the voxel level for a spatial extent of at least 10 voxels. vmPFC (4, 48, −8) activation based on the interaction between group and character. (B) The mean for parameter estimates at the cluster denoting vmPFC activation based on the interaction between group and character (autistic characters for the ASD group and non-autistic characters for the TD group). Dark orange bars denote judgments for autistic characters; light blue bars denote judgments for non-autistic characters. Error bars indicate standard errors. *$P < 0.05$. (C) Plots of correlations ($r = 0.43$, $P < 0.05$) between AQ scores and vmPFC activation during judgments for autistic characters in the interaction between group and character. Black circles indicate individuals with ASD ($n = 15$); white circles indicate TD individuals ($n = 15$).

without autistic traits (Figure 3A and B). *Post hoc* tests were performed on the parameter estimates.

Functional connectivity results

In individuals with ASD as well as TD individuals, the vmPFC and other areas were activated during self-processing. However, this leaves the question of whether there are differences between individuals with ASD and TD individuals in terms of network connectivity in these brain areas. To address this, group differences in functional connectivity were assessed (Table 4). Results were thresholded at $P < 0.001$ (uncorrected) for a spatial extent of at least 10 voxels. Compared with TD participants, those with ASD showed greater functional connectivity between the vmPFC and anterior cingulate, the vmPFC and thalamus and the vmPFC and middle cingulate during autistic character judgments.

In contrast, compared with ASD participants, TD participants showed greater functional connectivity between the vmPFC and IFG, the vmPFC and precentral gyrus, the vmPFC and dorsolateral prefrontal cortex, the vmPFC and superior temporal gyrus (STG), the vmPFC and dorsomedial prefrontal cortex and the vmPFC and middle frontal gyrus during non-autistic character judgments.

DISCUSSION

Rating data for self- and other judgments

According to the behavioral results, the ASD group provided Yes responses for autistic characters more than the TD group did, whereas the TD group provided Yes responses for non-autistic characters more than the ASD group did. Thus, ASD and TD groups responded with affirmative answers to characters similar to themselves. However, the ASD group did not answer Yes for autistic characters more frequently than they did for non-autistic characters, whereas the TD group answered Yes for non-autistic characters more frequently than they did for autistic characters.

Subjective measurement may not be suitable for individuals with ASD. SRS can provide ratings from parents, teachers, spouses, other relatives or friends; it is difficult for individuals with ASD to monitor themselves using self-report scales.[2] These results reflect a relative lack of self-awareness in ASD (Toichi *et al.*, 2002). For example, children with ASD exhibit less self-consciousness; furthermore, autobiographical memories, which are experienced by the self, are remembered less well compared with events happening to others (Millward *et al.*, 2000; Bruck *et al.*, 2007; Lind, 2010; Williams and Happé, 2010). Additionally, the self-reference effect in memory is reduced in adults with ASD (Toichi *et al.*, 2002; Lombardo *et al.*, 2007). Taken together, these findings indicate that the strong differentiation observed in the TD group and the total lack of differentiation observed in the ASD group are both well supported.

We found no significant differences between the ASD and TD groups with regard to reaction times, and reaction times for other judgments were longer than those for self-judgments in both groups. Thus, for both groups, the cognitive load was greater for other judgments than for self-judgments. Our similarity hypothesis was not supported by the behavioral data in that selective responses toward similar targets were not observed.

Interaction between group and character

To address the question of whether individuals with ASD show specific responses for others with ASD, the interaction between group (with or

[2] Adults can also rate themselves using the optional Adult (self-report) Form in SRS 2 (Constantino and Gruber, 2012).

Table 4 Seed to voxel functional connectivity analyses based on vmPFC as seed region

	Region	BA	Cluster size	*T*	MNI coordinates		
					X	*y*	*z*
ASD group > TD group							
Self ASD and other ASD	Anterior cingulate	32	86	5.50	−14	20	34
	Thalamus		20	4.10	−10	−2	6
	Middle cingulate	24	12	3.83	12	8	36
Self non-ASD and other non-ASD	IFG	47	54	4.27	−30	38	−10
	Middle occipital	19	24	4.01	36	−70	8
	Claustrum		16	3.93	30	14	6
TD group > ASD group							
Self ASD and other ASD	IFG	45	235	5.06	−46	24	20
	dlPFC	46	235	4.63	−44	32	20
	IFG	44	27	4.82	64	10	10
	MFG	6	62	4.57	−26	12	68
	MFG	6	27	4.56	30	14	56
	Cerebellum		18	4.23	−54	−60	−38
	IFG	44	15	3.66	−56	10	6
Self non-ASD and other non-ASD	IFG	44	146	5.10	−60	12	16
	Precentral gyrus	6		4.00	−64	0	12
	dlPFC	9	86	4.68	48	14	38
	STG	22	14	4.04	−68	−20	0
	dmPFC	8	12	3.93	2	28	44
	MFG	6	20	3.74	32	12	60
	dlPFC	46	13	3.68	46	28	24

BA = Brodmann area; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; MFG = middle frontal gyrus.
Self ASD = self-judgments for autistic characters; other ASD = other judgments for autistic characters; self non-ASD = self-judgments for non-autistic characters; other non-ASD = other judgments for non-autistic characters.
$P < 0.001$, uncorrected at the voxel level for a spatial extent of at least 10 voxels.

without ASD) and character (autistic or non-autistic) must be examined.[3] The two-way interaction (group × character) was evaluated. According to the activation data for the interaction between group and character, the vmPFC was activated in the ASD and TD groups during self- and other judgments when the ASD group judged characters with autistic traits and the TD group judged characters without autistic traits. The findings of this study suggest that both individuals with ASD and TD individuals make selective neural responses toward others who are similar to themselves. Although individuals with ASD showed a relative lack of self-consciousness in their explicit subjective ratings, the selective activation in response to similar others with ASD reflected in the brain imaging data may suggest an implicit identification with similar others.

According to previous studies with ASD and TD participants, the vmPFC distinguished between self- and other evaluations in TD adults but not in individuals with ASD (Lombardo *et al.*, 2010a; Pfeifer *et al.*, 2013). However, these previous studies used a fictional character (Harry Potter) as the other target, and this character was not similar to the participants. In this study, the vmPFC activations in both ASD and TD groups were significantly greater when judging matched (autistic characters for individuals with ASD and non-autistic characters for TD individuals) than mismatched targets (autistic characters for TD individuals and non-autistic characters for individuals with ASD). Thus, individuals with ASD did not have vmPFC dysfunction in terms of the ability to distinguish between the self and another person, and the vmPFC seemed to underpin the ability to make distinctions between ASD and TD targets.

Another previous study also found that vmPFC activation did not distinguish between self- and other judgments in adults with ASD (Kennedy and Courchesne, 2008), although the 'other' used in this design was someone with whom participants were likely to be very close: their mother. The vmPFC activation is related to processing similar others (Schmitz *et al.*, 2004; Ochsner *et al.*, 2005; Jenkins *et al.*, 2008; Chen *et al.*, 2010; Krienen *et al.*, 2010), which is consistent with our finding that the vmPFC was activated in response to the self and similar others in both the TD group and the ASD group.

It is important to note that the IFG, postcentral gyrus, paracentral lobule, precuneus, cuneus, lingual gyrus, cerebellum, fusiform and SFG, as well as vmPFC were activated during this study. All these areas were larger clusters than the vmPFC. Although this study focused on the vmPFC funtion, future studies need to further investigate the functions of these areas.

Differences in connectivity

According to the functional connectivity results, frontal–posterior connectivity (Just *et al.*, 2012) was observed in TD individuals, but not in individuals with ASD, during similar judgments (autistic judgments in the ASD group and non-autistic judgments in the TD group). The present findings reflect differences in the type of brain connectivity exhibited by the ASD and TD groups. Although the activation results for both groups revealed that the vmPFC was activated in response to similar others, the functional connectivity results reflected a specific network in each group, i.e. responses in individuals with ASD toward autistic characters and responses in TD individuals toward non-autistic characters. Although empathic responses in TD individuals are based on collaboration between frontal (the vmPFC as the area for self-representation) and posterior (the STG; Wernicke's area for language processing) areas, empathic responses in individuals with ASD are based on collaboration within frontal areas.

Several previous studies have demonstrated a lack of empathy and deficits in self-related representation, in ASD (Greimel *et al.*, 2010; Lombardo *et al.*, 2010; Schulte-Rüther *et al.*, 2011). However, previous studies also showed that it was difficult for those with ASD to assume the perspectives of TD others. To our knowledge, few studies have employed characters with and without autistic traits as target stimuli (Komeda *et al.*, 2013a). It is difficult for TD individuals to understand others who are dissimilar from themselves (Komeda *et al.*, 2013b). Thus, it is not surprising that it is also difficult for those with ASD to understand TD individuals. This is the first empirical study to investigate the empathy of ASD individuals for others with autistic traits (for a review, Dern, 2008). Individuals with ASD are likely to empathize with other people with ASD. Empathy varies as a function of similarity between participants and characters (Komeda *et al.*, 2013b). Individuals with ASD and TD individuals with high levels of autistic traits, even if they have not been diagnosed with ASD, are likely to better understand others with autism. Interestingly, even when characters had autistic traits, individuals with ASD seemingly did not use the frontal–posterior network during self- and other judgments.

CONCLUSION

Individuals with ASD do not lack empathy toward others who are similar to themselves, just as TD individuals respond selectively to others who are similar than to those who are dissimilar. In contrast, the neural mechanisms underlying the responses of those with ASD to others differ from those underlying this process in TD individuals. Individuals with ASD do not employ the frontal–posterior network during cognitions pertaining to the behavior of other ASD individuals.

[3] The regressors include both Yes and No responses. We conducted analyses based on participants' individual responses. However, vmPFC activation was not observed because subjective measurement was not suitable for individuals with ASD.

Because these findings explain the characteristics of individuals with ASD, they may also contribute to improving special needs education, educational interventions and developmental support for individuals with autism (Åsberg, 2010; Åsberg and Sandberg, 2010). In terms of clinical implications, the present findings suggest that people with ASD characteristics would be able to help people with ASD. In terms of education, this study carries implications for the development of curricula for special needs classes.

Conflict of Interest

None declared.

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Case report

Quetiapine responsive catatonia in an autistic patient with comorbid bipolar disorder and idiopathic basal ganglia calcification

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Abstract

Background: Bipolar disorder (BD) has been linked with the manifestation of catatonia in subjects with autism spectrum disorders (ASD). Idiopathic basal ganglia calcification (IBGC) is characterized by movement disorders and various neuropsychiatric disturbances including mood disorder. *Case*: We present a patient with ASD and IBGC who developed catatonia presenting with prominent dystonic feature caused by comorbid BD, which was treated effectively with quetiapine. *Conclusion*: In addition to considering the possibility of neurodegenerative disease, careful psychiatric interventions are important to avoid overlooking treatable catatonia associated with BD in cases of ASD presenting with both prominent dystonic features and apparent fluctuation of the mood state.

Keywords: Bipolar disorder; Quetiapine; Autism; Catatonia; Dystonia; Basal ganglia calcification

1. Introduction

Catatonia, characterized by abnormalities of speech, movement and behavior, has been increasingly recognized as a comorbid syndrome of subjects with autism spectrum disorders (ASD) [1]. Comorbid psychiatric disorders such as depression and bipolar disorder (BD) have been linked with the manifestation of catatonia in ASD [1]. High prevalence of BD has been reported in subjects with ASD [2]. Therefore, individuals with ASD presenting with comorbid BD might be at increased risk for catatonia.

Idiopathic basal ganglia calcification (IBGC) is a genetically and clinically heterogeneous condition that is characterized by movement disorders and various neuropsychiatric disturbances including few cases of organic BD [3].

This report describes a 17-year-old patient with autistic disorder and idiopathic basal ganglia calcification who developed dystonia-like catatonia associated with comorbid bipolar disorder, which was treated effectively with quetiapine.

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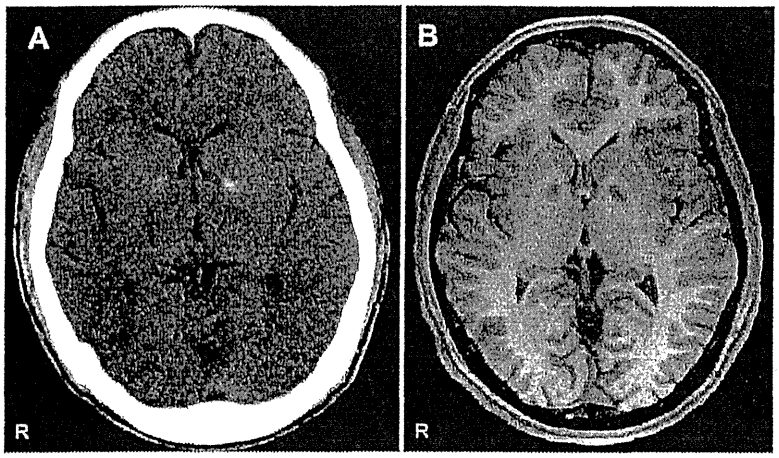

Fig. 1. (A) Cerebral CT scan showing intense bilateral symmetrical calcification in the basal ganglia. (B) Cerebral MRI showing hypointensity in the bilateral basal ganglia on T1-weighted image.

2. Case report

A 17-year-old boy with autistic disorder was admitted to our psychiatric department because of his six-month history of progressive decline in overall function with dystonic posture. At age 3, he was diagnosed as having autistic disorder and severe mental retardation because of his lack of social responsiveness, repetitive behavior, and language delay. He attended a special educational program for children with ASD during his school years and was well-adjusted. At age 16, about a year before admission, he had developed aggressive behavior such as kicking doors and shouting in various situations with no clear psychosocial event. In addition, decreased need for sleep and increased appetite were observed for about one month. Subsequently, during the next half year, he gradually lost his self-care skills in daily life. He developed food refusal, showed resistance to eating and lost 20 kg of weight during the subsequent half year. His interaction with others gradually decreased and he became progressively mute. He would not engage even in activities of his own specific interest. Additionally, he developed dystonic posture of his right hand, which gradually progressed to the upper extremities. He required assistance during washing and dressing. Eventually, he required support even to remain sitting. He was referred to the pediatric department because of progressive motor disturbance. He showed no motor weakness or cranial nerve involvement. No rigidity, tremor or primitive reflex was detected. His other systemic examinations were normal except for progressive dystonic feature and slowing of overall movements. Electromyography, EEG, nerve conduction velocity examinations all yielded normal results. Extensive etiological explorations, including laboratory and clinical examination, also gave normal results. Cerebral computerized tomography (CT) scanning revealed calcifications in bilateral basal ganglia (Fig. 1). Cerebral magnetic resonance imaging (MRI) shows hypointensity in the corresponding area only on a T1-weighted image (Fig. 1). Despite further extensive investigations, the etiology of his basal ganglia lesions remained unclear. He was treated predominantly as a neurological case because of prominent dystonic features. Trials of levodopa and anticholinergic agents failed to alleviate his symptoms. After showing progressive decline in overall function, he was referred to our department. On admission, he was mute, giving no response to questions, and showing no interest in his surroundings. Dystonic posture of the upper body was observed. It was particularly severe on the right hand. Based on his symptoms, he was diagnosed with catatonia associated with possible BD. Two weeks after admission, he again developed aggressive behaviors with increased appetite and speech. Risperidone and aripiprazole were administered in this order, but both medications were discontinued because of oversedation and severe extrapyramidal symptoms. Subsequently, quetiapine monotherapy was initiated with a dosage of 300 mg/day. One week after starting quetiapine administration, his violent behaviors and catatonia symptoms including dystonic posture resolved dramatically. He has been independent with his ADLs for more than one year without apparent mood changes or worsening of catatonia. These effects of quetiapine have continued with no adverse event.

3. Discussion

This case report is the first of a patient with autistic disorder with IBGC who showed catatonia presenting with prominent dystonic feature caused by mood disturbances, with dramatic improvement by quetiapine administration.

In this case, neurodegenerative disease, not catatonia, was first suspected because progressive dystonia-like deterioration was the most prominent symptom of this patient catatonia. IBGC might have rendered the patient exceptionally vulnerable to mood disturbance, which engenders catatonia presenting with prominent dystonic features. This vulnerability should also be borne in mind, especially for ASD subjects with IBGC, when prescribing antipsychotics such as risperidone and aripiprazole, each of which has higher affinity for dopamine D2 receptor than quetiapine has.

Our case shows a challenge in the diagnosis of comorbid BD because of the presence of limited verbal skills. However, the diagnosis of affective disorders can be supported by observation of changes in behaviors and functioning from the baseline in subjects with limited verbal skills [4]. In this case, an apparent change was observed in appetite, overall behaviors, and dystonic features in the absence of clear psychosocial events, which suggests comorbid BD. The effect of quetiapine observed in our case might lend indirect evidence that various fluctuating symptoms were more related to comorbid BD, although positive response to quetiapine, a first line treatment of BD, does not itself indicate BD. Although it remains unclear whether his fluctuating symptoms resulted from organic BD caused by IBGC or idiopathic BD, other psychotropic agents with mood stabilizing properties might also have ameliorated his symptoms.

In addition to considering the possibility of neurodegenerative disease such as IBGC, careful psychiatric interventions are extremely important to avoid overlooking treatable catatonia associated with mood disorder in cases of ASD presenting with both prominent dystonic features and apparent fluctuation of the mood state.

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Conflict of interest

The authors declare no conflict of interest.

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特集I 自閉症

自閉症の症候*

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Key Words：autism spectrum disorder (ASD), co-morbidity

はじめに

自閉症(自閉性障害)は米国精神医学会の『精神疾患の診断・統計マニュアル』(DSM-IV)により，①対人的相互反応における質的障害，②コミュニケーションの質的障害，③行動・興味・活動の限局された反復的・常同的な様式の三つの主要徴候が3歳までに出現する発達障害と定義され，Asperger障害，特定不能の広汎性発達障害とともに「広汎性発達障害」として分類されていた[1]．2013年5月に改定されたDSM-5では，自閉症，Asperger障害，特定不能の広汎性発達障害などの下位診断群を包含する概念として，自閉スペクトラム症/自閉症スペクトラム障害(autism spectrum disorder：以下，ASD)が採用され，A)複数の状況下における社会的コミュニケーションおよび対人的相互反応の持続的な欠陥，B)行動・興味・活動の限局された反復的・常同的な様式の二つの主要徴候が幼少期早期に出現するものと定義された[2]．すなわち，現行のDSM-5では，自閉性障害やAsperger障害などの下位分類は廃止されたため，本稿で用いる自閉症という用語は，特にことわりのない限りASDカテゴリー全体を示すものとする．ASDでは上記の主要徴候に加え，多動・不注意，不器用，てんかんなどさまざまな併存症を伴い，これらのASDに非特異的症状も含めて，ASDにおける臨床症状の多様性，ひいては大きな個人差を形成しており，臨床的に重要である[3]．本稿では主要徴候に加え，併存症についても概説する．さらに，鑑別診断の観点から，神経内科領域の疾患との関連についても言及する．

ASDの主要徴候

DSM-5では，ASDの主要徴候は下記A)，B)の2領域における症状より構成される[2]．DSM-5では，ASDと診断されるには下記A)，B)に示した主要徴候をすべて有することが必要とされ，拡大しすぎた自閉症概念からより古典的な自閉症概念に回帰したといえる．以下，項目を分けて具体例を示す．

A. 複数の状況下における社会的コミュニケーションおよび対人的相互反応の持続的な欠陥

a. 相互の対人的―情緒的関係の欠陥

他者と適切な距離感を持って接することが困難である．他者と興味や感情を共有することが少ない．自身の関心事のみに話が集中し，会話が一方通行になりやすい．

* Symptoms of ASD.

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b. 対人的相互反応で非言語性コミュニケーション行動を用いることの欠陥

アイコンタクトや身振り，顔の表情などの非言語的手段を適切に用いたコミュニケーションが不得手である．

c. 人間関係を発展させ，維持し，それを理解することの欠陥

さまざまな社会的状況に応じ臨機応変に振る舞うことが困難(場の空気を読むのが苦手)である．想像上の遊びを他者とともにすることが困難である．他者に対する興味の欠如から友人関係を構築することが困難である．

これらの対人的障害は乳幼児期から現れ，ライフコースを通じて持続するが，その現れ方は発達とともに変化することに注意を要する[4]．通常，ASDは幼児期に診断される．臨床的には2歳頃には言語以前のノンバーバルな対人行動の異常によって診断可能であるが，発語が早い平均知能ケースでは見逃され，診断が遅れる傾向がある．これは，この時期の親はことばの遅れを心配するのに対して，アイコンタクト，指さし，ジェスチャーなどのノンバーバルなコミュニケーションをあまり意識しないため，問題とされにくいためである．したがって，問診でも回顧されにくい．児童期には明らかになりにくかった対人的障害が，社会的要請が高くなる青年期以降，顕在化し，成人期にかけて初めて診断を受けるケースは近年注目されている[5]．DSM-5ではこうしたケースの診断・治療においては，「詳細な発達歴の聴取が困難な例がありえるので，自己申告された(生活上の)困難さを考慮することが重要である」と明記されている[2]．

ASDにおける対人的障害の神経基盤の一つとして，「社会的認知機能」の障害が想定されている[6]．社会的認知機能とは，他者の表情，声のトーン，身振りなどの対人コミュニケーションに必要な情報を正確に処理し，適切な対人交流を可能とするのに必要な機能とされており，表情認知課題や他者心理推測課題を用いた脳機能画像研究などから，扁桃体・上側頭溝領域・前頭葉腹内側部などの複数の脳領域間のネットワーク障害が関与していると考えられている[6][7]．

B. 行動・興味・活動の限局された反復的・常同的な様式

a. 常同的または反復的な身体の運動，物の使用，または会話

単純な常同運動(例：手を叩く，指を弾く)や反復的な物の使用(例：おもちゃを一列に並べる)を認める．反響言語．

b. 同一性への固執，習慣への頑ななこだわり，または言語的・非言語的な儀式的行動様式

小さな変化に対する極度の苦痛(例：ルーチンとしていることに突然の変更などが加わると抵抗を示し，時にパニック状態に陥る)．思考における柔軟性のなさ．儀式的行為(例：儀式的な挨拶，毎日同じ道順を辿る，毎日同じ食物を食べる)．

c. 強度または対象において異常なほど，きわめて限定された執着する興味

一般的ではない対象への強い愛着または没頭(例：鍋や掃除機に強く引きつけられる幼児)や過度に限局または固執した興味(例：鉄道の時刻表を何時間もかけて書き出す成人)など．

d. 感覚刺激に対する過敏または鈍感さ，または環境の感覚的側面に対する並外れた興味

痛み刺激に過度に反応する(例：注射を過剰に恐れる)，特定の音に対する敏感さ(例：子どもの泣き声を非常に苦痛に感じる)，外気温の変化への関心のなさ(例：通年で冬服を着続ける)，対象を過度に嗅いだり触れたりする，光や一定の動きをするものを見ることに熱中するなど．

以上のような限局的反復行動は，知能レベルにかかわらず1歳6カ月までに現れ[8]，その出現頻度はASD児の約8割のケースで年齢によらずほぼ変わらないことが示されている[9]．つまり，限局的反復行動は対人的障害と同様，乳幼児期から現れ，発達とともにその様相を変化させながらライフコースを通じて持続する．また，その現れ方も多種多様であり，反響言語や目の前で手をひらひらさせる行動を示す知的障害を合併するASD児から，決まったルーチンを毎日かかさずにやらずにはいられないASD成人までさまざまである[10]．また，DSM-IVに含まれておらず，新たにDSM-5に含まれたB)の診断基準の一つに，「感覚刺激への過剰または過小な反応，あ

るいは，周囲の感覚的側面に通常とは異なる反応を示す」がある．実際，感覚刺激への異常反応はしばしば限局的反復行動とも関連し，年齢にかかわらず日常生活上さまざまな場面で支障をきたすことが多い[10]．

限局的反復行動の背景については，対人的障害に比べて研究が乏しいが，その一つに実行機能(executive function：EF)の障害が指摘されている[11]．EFはplanning，刺激への反応を抑制する能力(inhibition)，認知の柔軟性(cognitive flexibility)，作動記憶(working memory)など複数の要素からなり，効率的な課題遂行を可能にするために重要な機能である[12]．実際ASD者は，日常生活のさまざまな場面においてEFの障害と関連した困難さを抱えていることがしばしば観察される．Shafritzら[13]は，高機能ASDの成人18名とコントロール群15名を対象に，「四角形・円形・三角形」の3種類の図形判断をcognitive set shifting課題とし，課題施行中の脳活動変化をfMRIにより探索した．結果，ASD群では課題成績の正確さはコントロール群に比べて低く，またASD群においてADI-R(Autism Diagnostic Interview-Revised)で評価された限局的反復行動の症状程度は，前部帯状回の賦活と負の相関があったと報告している．感覚刺激への異常反応の背景機序については，EEG・MEG・fMRIなどの神経生理学的指標を用いた研究がこれまでいくつかなされているが，統一した見解は得られていない[14]．高橋ら[15][16]は，聴覚刺激に対する驚愕反応(聴覚性驚愕反応；acoustic startle response：ASR)を評価する手法により，ASD児では定型発達児に比べて，通常のASR検査では用いない微弱な音圧の聴覚刺激に対して有意に大きな驚愕反応を示し，反応潜時も有意に延長したことを明らかにしている．また，ASRで得られた神経生理学的指標と対人応答性尺度(Social Responsiveness Scale：SRS)で評価された自閉症的特性の高さと有意な相関があることが示された．このことは，感覚刺激に関する生物学的指標が，ASDの中間表現型や治療介入の効果判定指標となる可能性を示唆している[14]．

これまでASDの病態については，言語機能，遂行機能，注意機能，社会的認知機能などさまざまな仮説が提案されてきたが，どの単一の仮説もASDのすべての側面を統一的に説明しえず[17]，むしろ，複数の神経心理学的特性が組み合わさってASD各個人の臨床特性を形成していると考えられる．このことは，複数の脳内ネットワークがその病態形成に関与しているという近年の脳画像研究で得られた知見と矛盾しない[7]．さらにいえば，診断横断的に複数の精神神経疾患と重複する病態が存在する可能性が，近年のゲノム研究からも示唆されている[18]．

ASDの主要徴候と神経内科領域の疾患との関連性および鑑別について

ASDの主要徴候の病態形成に関与する脳領域になんらかの障害をひき起こす神経変性疾患や脳血管障害においては，ASDの主要徴候と類似した症候がみられることが知られている．成人期に初めてASDを診断する際には，こうした神経内科領域の疾患を鑑別する必要がある．たとえばParkinson病では，社会的認知機能障害が非運動症状の一つとして出現することが知られており，表情認知課題や他者心理推測課題を用いた研究においてもその障害が示唆されている[19]．また，反復行動がParkinson病患者で多くみられることも指摘されている[19]．ただし，横断的には類似していても両者では経過が異なるため，成人患者にみられる社会的認知機能障害や反復行動が，幼少期より持続して認めるものか，またはParkinson病の非運動症状としての発現(後天的要素)あるいはそれに伴う従来性向の増悪なのかについて，児童期の発達歴や性格傾向に関する情報収集に基づいて判断する必要がある．前述したように，知的障害がないケースでは，ASD症状があっても保護的環境下では適応不良が目立たないことが少なくないからである．ただ，ていねいにエピソードを聴取することで鑑別のヒントになる可能性がある．また，認知症では記銘力障害以外に，こだわりの増強・社会的問題行動・気分障害や不安障害などがbehavioral and psychological symptoms of dementia(BPSD)として表出するが[20]，BPSDとされる症状も認知症発症以前から有していたASD特性として解釈可能なものか，認知症に伴って発現した症状なの

かを鑑別する必要がある．ただし，元来のASD特性が認知症発症によってさまざまな形に修飾されることもあり，上述のような精神疾患に加え，BPSDとの鑑別に注意を要した症例が報告されている[21)22)]．荻原ら[22)]は，長期間持続する汎不安状態を主訴とし，82歳時に初めてASDを疑われた老年女性の1例を報告している．この症例では，75歳時に夫が急死して以降，全般性不安，長時間繰り返す手洗いなどを認めるようになり，当初は遷延性の老年期うつ病や認知症の初期が疑われていたが，気分変動が状況依存的であり，認知機能も良好に保たれていた．その後，発達障害の存在を疑った家人より詳細かつ的確な生活情報が得られたことにより，そのASD特性が明らかとなり，ASD特性を念頭においた環境調整により情動的な安定が得られ，生活習慣を構造化することで退院後も施設内で落ち着いた生活を送れるようになったと報告している．ASD特性を有する高齢者では，その特性を考慮した適切な環境調整により，さまざまな症状が軽減できる可能性を示している．ASDの有病率の高さ(成人におけるASDの有病率は少なく見積もって約1%)や閾下のASD特性を有する者が高頻度(約1割)で存在する事実を考えると，認知症をはじめとする老年期診療においてもASD特性を考慮することはその後の治療に有意義である[23)]．しかし現在，老年期のASDに関するエビデンスは非常に乏しく，この問題の解決に向けた有病率，診断手法，加齢に伴う症候の変化などに関するエビデンスの蓄積が今後の課題とされている[23)]．英国ではThe National Autistic Society (NAS)が中心となり，上記問題解決に向けた研究がすでに開始されており，老年期のASDの社会的サービスの利用率や介助者の有無に関する調査が行われている．

ASDの併存症

ASDの児童および成人では，約70%の症例で一つ以上の精神科的または身体的併存症が認められる[3)]．その併存症の特性や重症度が各ASD個人の予後を大きく左右する因子ともなる．また，これらの併存症は主要徴候と複合的に関与しながら各ASD個人の多彩な臨床像を形成するため，主要徴候のみならず併存症も的確に把握することがASD臨床において重要である．

1．精神科的併存症

ASDにみられる精神科的併存症は，知的障害・注意欠如多動性障害・強迫性障害・チック・抑うつ状態・双極性障害・パニック・癇癪・被害関係妄想・幻覚体験(フラッシュバック体験)・カタトニア(→詳細は後述する)・不安障害(限局性恐怖症，社会不安障害)など非常に多岐にわたる．これらの精神科的併存症はASDと合併率が高いことが知られている精神疾患も含まれるが，状況因に反応して発現する場合も多く，その評価は幼少期からの発達経過を含めた包括的なものとする必要がある[3)]．これら併存症の中には，神経内科領域の疾患と類似した症候を呈し鑑別を要するものがある．代表的な症候として2例を示す．第一に，ASDで時にみられる被害関係妄想や幻覚体験などの統合失調症様症状があげられる[24)]．これは，いじめや環境への不適応を契機に被害的な認知に傾いてしまうことや，ASD特有の固執性の言動や反響言語が統合失調症に特徴的な徴候(対話性幻聴，独語)と誤って判断されることなどが要因となる．よって，統合失調症や辺縁系脳炎による精神病症状との鑑別がしばしば必要となる．また，実際に，いずれかの鑑別だけでなく，ASDに辺縁系脳炎が合併した症例も報告されており，注意が必要である．第二に，ASDの青年期に好発するカタトニアがあげられる．カタトニアの基本症状は，i)運動と言葉の緩慢化，ii)活動を開始したり，完遂することの困難さ，iii)他者による身体的あるいは言語的な促しに依存することの増加，iv)受動性の増加と自発性低下の4つであり，カタトニアにしばしば伴う症状として，昼夜逆転，反復的儀式行動の増加，Parkinson様症状，興奮，不安焦燥がある[25)]．ASDにおけるカタトニア出現の背景因子は，なんらかの外的要因(ストレス，急激な生活状況の変化など)による限局的反復行動の増悪や気分障害の合併などさまざまである[25)]．昏迷状態となり全身管理が必要となったASD症例も報告されており[26)]，辺縁系脳炎などとの鑑別を要する場合がある．青年期にカタトニアを認めた症例では，器質性疾患の除外とともに，ASDをベー

スにカタトニアが出現している可能性も考慮する必要がある．

2．身体的併存症

ASDでは，運動協調面の異常・睡眠障害・てんかんなどの“neurological comorbidities”が認められることも多い[27]．これらはASD個人の全般的機能への影響も大きく，また介入により改善する可能性も高いため，的確に評価することが重要である．

ASDにおける運動面の異常は歩行・協調運動などにおいて観察され[28]，乳幼児期の早期徴候の候補の一つとしても注目されている．ASD児の歩行をmotion analyzerで評価した研究では，スムーズな歩行ができないことや歩行時の姿勢保持の困難さが示唆されているが[29]，標準的検査法が確立されておらず，その実態や機序はまだよくわかっていない．睡眠障害はASDにおいて40～80％とほかの発達障害に比べても高率にみられ，常同行為の増加や社会的スキルの低下など日常の生活機能にも多大な影響を及ぼす．ASDにおける睡眠障害の特徴としては，入眠困難や睡眠維持の困難が報告されている[27]．てんかんは，近年のメタアナリシスによると，知的障害を有するASDでは21.4％，知的障害のないASDで8％の合併率が報告されている[30]．ASDに特有の発作型は特定されておらず，好発年齢は幼少期と青年期に二峰性のピークがある[27]．

最後に

自閉スペクトラム症/自閉症スペクトラム障害(ASD)では主要徴候に加え，多彩な身体的・精神的併存症がみられ，発達過程や生活環境との相互作用によりさまざまな臨床特性を呈する．また，知的障害のない人では社会適応の破綻が成人になって，あるいは成人期のライフイベント後に初めて現れるケースも少なくないが，このようなケースでは幼少期の発達歴情報が入手困難なことがしばしばある．このため，ASDの診断には発達歴・生活歴を含め，現症に関しても精神医学的評価に加え，神経学的異常所見の有無などの身体疾患の評価も含めたmulti-dimensionalな評価が必要となる．特に，成人期以降の患者においては，一見したところ神経内科疾患でみられる症状が前景にあるとASDの主要徴候が見逃されやすいため，精神科あるいは小児科との診療科を超えた連携が重要となってくるであろう．また，今日ASDの研究は，児童・青年期を主体としたものであり，成人期以降，とりわけ老年期に関してはエビデンスが乏しい．今後，特殊な介護ニーズを有する「老年期ASD」の研究・診療体制の構築は高齢化社会を迎える本邦において重要なテーマの一つと考えられる．

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