

Table 1 Level-one screeners of autism spectrum disorder targeting total population examined by follow-up studies

Screening tool	Author	Sample/N	Age (months)	First-stage screening	Second-stage screening	True-positive cases (N)	Age at follow-up	Rescreening	Local clinicians' diagnosis	Case ascertainment (N/diagnostic criteria)	Sensitivity, specificity, positive predictive value
Checklist for Autism in Toddlers (CHAT)	Baird et al. (2000)	General population/ 16,235	18 (routine health developmental check)	Parent questionnaire (9 items) + professional observation (5 items)	Repeated same format as at first-stage screening on 60 children 1 month later	10/high-risk threshold 20/medium-risk threshold	7–8 years	Checklist for referral at 3.5 years, Pervasive Developmental Disorder Questionnaire at 5.5 years	Included	94/CD-10, (ADI-R)	Two-stage screening high-risk threshold: sens 0.11, spec 1.00, PPV 0.83 medium-risk threshold: sens 0.21, spec 1.00, PPV 0.59
Early Screening of Autistic Traits Questionnaire (ESAT)	Dietz et al. (2006)	General population/ 31,724	14–15 (well-baby clinic attendance)	Parental interview (4 items) by physicians at well-baby clinics	Parental questionnaire (14 items) + professional observation (NR) on 255 children on a home visit 1–2 months later	18	Average 43.1 months (SD=5.2)	Parental questionnaire at 2 (NR) and 4 years (incorporating the Autism Screening Questionnaire)	Not included (all cases were diagnosed by the research team)	DSM-IV, ADOS	Two-stage screening: sens NR, spec NR, PPV 0.25 (this figure was calculated at the first evaluation at 23.3 months)

(continued)

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Modified Checklist for Autism in Toddlers (M-CHAT)	Kleinman et al. (2008)	Low-risk sample/ 1,160, high-risk sample/ 256	16–30 (well-baby clinic attendance)	Parental questionnaire (23 items)	Follow-up telephone interview 1–2 months later	Low-risk sample/ 20, high-risk sample/ 117	Average 32.2 months (SD=8.0)	Rescreening 2 years later	Not included (all cases were diagnosed by the research team)	DSM-IV, ADOS, ADI-R, CARS	Two-stage screening: PPV 0.59 (mixed sample of low risk and high risk)
Japanese Version of the Modified Checklist for Autism in Toddlers (M-CHAT-JV)	Kamio et al. (2013a)	General population/ 1,851	18 (routine health checkup)	Parental questionnaire (23 items)	Follow-up telephone interview on 195 children 1–2 months later	Twenty	Average 49.4 months (SD = 11.5)	Parental questionnaire and interview + professional examination at 3 years (routine health checkup), direct interview and observation at 5 years (school entry health checkup)	Included	51/DSM-IV-TR, CARS, ADI-R, ADOS	Two-stage screening: sens 0.48, spec 0.99, PPV 0.46, likelihood ratio 33.4

prescreened at well-baby clinics using the 4-item ESAT (interest in different toys, varied play, readability of emotions, reaction to sensory stimuli). Any child found to be positive on the prescreening then received the 14-item ESAT, completed by both the parent and a child psychologist during a home visit. This two-stage screening on 31,724 Dutch children identified 18 children who were diagnosed with ASD at a mean age of 23.3 months, giving a PPV of 0.25. The high refusal rate at each of the screening stages might be due to the young age of the children.

Modified Checklist for Autism in Toddlers (M-CHAT)

The *M-CHAT* (Robins et al. 2001) is a 23-item parental questionnaire, created by adding to the key items of the CHAT new items covering a wide range of social behaviors, including social responsiveness, imitation, joint attention, and *social referencing*, as well as sensorimotor behaviors (Table 2). Validation has been repeatedly examined in a low-risk sample (Kleinman et al. 2008; Pandey et al. 2008a; Robins 2008). Its PPV was determined to be 0.59 from the follow-up data for a combined clinical and population-based sample (Kleinman et al. 2008) and 0.43–0.46 for a total population sample (Kamio et al. 2013a) as will be discussed in the next section.

Two-Stage Screening Using the M-CHAT at Routine Health Checkups in Japan

In Japan, screening at 18 months of age is easy from a practical standpoint because almost all Japanese children receive a regular health checkup at that time under the Maternal and Child Health Act. M-CHAT questions translated into Japanese are used with a lowered threshold alongside illustrations (Fig. 1). Because few typically developing children aged 18 months lack joint attention behaviors and *pretend play* that constitute the M-CHAT's key items (Fig. 2; Inada et al. 2010), failing the M-CHAT at 18 months of age is an alarm bell that something is not right with the child's *social development*.

A two-stage screening of 1,851 children using the Japanese version of the M-CHAT (M-CHAT-JV; Inada et al. 2011a) identified 20 children with ASD at age 2 (14 boys (70%), 8 HFASD (40%)) among 51 children who were finally identified to have ASD by 3 years or older (range 3–6 years) in the cohort. This gave the M-CHAT-JV a sensitivity of 0.48, a specificity of 0.99, a PPV of 45.5%, and a *likelihood ratio* of 33.4 for ASD diagnosis. Sixteen of twenty-two *false-negative* cases (73%) had normal-range IQs or superior IQs (Kamio et al. 2013a).

The items that best identified ASD in the Japanese community sample were declarative pointing, follows a point, brings to show, pretend play, response to name, imitation, follows a gaze, imperative pointing, and language comprehension (Inada et al. 2011a). When comparing these Japanese data with those from studies in the USA (Robins et al. 2010) and China (Wong et al. 2004), four items – pretend

Table 2 Modified Checklist for Autism in Toddlers (M-CHAT)

M-CHAT	
Please fill out the following about your child's usual behavior, and try to answer every question. If the behavior is rare (you've only seen it once or twice), please answer as if your child does <i>not</i> do it.	
1. Does your child enjoy being swung, bounced on your knee, etc.?	Yes No
2. Does your child take an interest in other children?	Yes No
3. Does your child like climbing on things, such as up stairs?	Yes No
4. Does your child enjoy playing peek-a-boo/hide-and-seek?	Yes No
5. Does your child ever pretend, for example, to talk on the phone or take care of a doll or pretend other things?	Yes No
6. Does your child ever use his/her index finger to point, to ask for something?	Yes No
7. Does your child ever use his/her index finger to point, to indicate interest in something?	Yes No
8. Can your child play properly with small toys (e.g. cars or blocks) without just mouthing, fiddling, or dropping them?	Yes No
9. Does your child ever bring objects over to you (parent) to show you something?	Yes No
10. Does your child look you in the eye for more than a second or two?	Yes No
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)	Yes No
12. Does your child smile in response to your face or your smile?	Yes No
13. Does your child imitate you? (e.g., you make a face-will your child imitate it?)	Yes No
14. Does your child respond to his/her name when you call?	Yes No
15. If you point at a toy across the room, does your child look at it?	Yes No
16. Does your child walk?	Yes No
17. Does your child look at things you are looking at?	Yes No
18. Does your child make unusual finger movements near his/her face?	Yes No
19. Does your child try to attract your attention to his/her own activity?	Yes No
20. Have you ever wondered if your child is deaf?	Yes No
21. Does your child understand what people say?	Yes No
22. Does your child sometimes stare at nothing or wander with no purpose?	Yes No
23. Does your child look at your face to check your reaction when faced with something unfamiliar?	Yes No

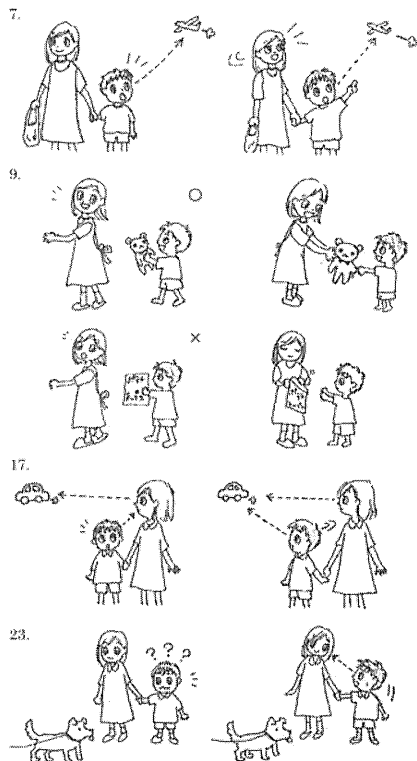
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The M-CHAT is reproduced here with permission from the authors and is from the official M-CHAT website (http://www2.gsu.edu/~psydlr/DianaLRobins/Official_M-CHAT_Website.html)

play, declarative pointing, brings to show, and follows a point – are found to be common items which are most sensitive to ASD among the three countries (Table 3). In addition, the response to name item is common in the USA and Japan, while the imitation item is common in China and Japan (Fig. 2).

This table lists the key facts of the Modified Checklist for Autism in Toddlers (M-CHAT) and includes its basic concept as a level-one screener, its successful

Fig. 1 Illustrations for items 7, 9, 17, and 23 are added to the Japanese version of the Modified Checklist for Autism in Toddlers (M-CHAT-IV). Illustrations for four items (7, declarative pointing; 9, brings to show; 17, gaze following; and 23, social reference) are added to the Japanese translation by Yoko Kamio. These items which are related to *joint attention* or social reference behaviors ask parents about negative symptoms (absence of a behavior expected to be present at this age is an alarm bell). These illustrations are designed to help parents understand the meaning of the questions



method of use, and its key items which are universal across countries. Data are cited from Robins et al. (2010), Wong et al. (2004), and Inada et al. (2011a).

Taking these findings together, the combination of M-CHAT screening and community developmental surveillance is a promising means of early detection of ASD in children with and without *developmental delay*. In addition, pretend play and *joint attention*, which are universal across countries, seem to be strong predictors of ASD diagnosis. If such screening is applied to 18-month-old children, primary care providers should introduce a *pre-diagnostic service* immediately after

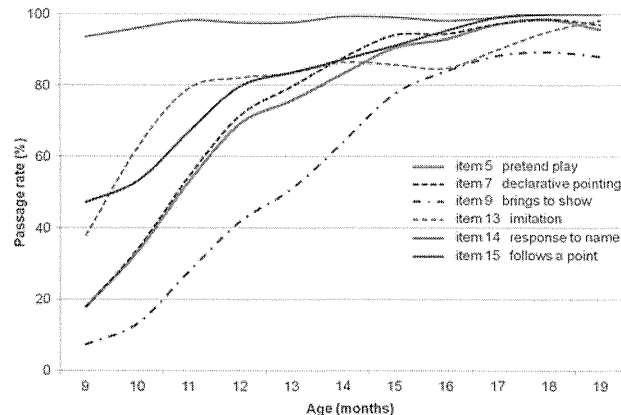


Fig. 2 Chronology of the emergence of social behaviors. Adjusted passage rate of the most sensitive *M-CHAT* items to ASD cross-culturally. This graph is created from data in Inada et al. (2010) with permission from the authors, using the raw passage rate $(P_{n+1} + 2 \times P_n + P_{n-1})/4$, where P_n is passage rate at n months

screening (e.g., small group activities) as these may be helpful for parents to learn more about their child with ASD.

Autism Spectrum: Future Directions and Issues

The new edition of the American Psychiatric Association's DSM-5 (American Psychiatric Association 2013), includes a new category of ASD which combines the DSM-IV categories of *autistic disorder*, *Asperger disorder*, and *pervasive developmental disorder-not otherwise specified (PDD-NOS)*. There is the assumption that an individual with clinical needs will not only be assigned to a diagnostic category but also be described in terms of his/her individual levels of symptom severity and general impairment (Happé 2011). Many individuals in the high-functioning subgroup, mostly classified as having PDD-NOS, do not show the full set of *autistic triad* impairments and thus will be near the end of the autism spectrum within the diagnostic label of ASD or will be labeled instead as having *social (pragmatic) communication disorder* (American Psychiatric Association 2013).

There is some evidence for the dimensional aspect of the autism spectrum. In Japan, a recent national survey was conducted with a large sample of children aged 6–15 years ($n = 22,529$) to examine symptom distribution in the general child population (Kamio et al. 2013b), using the Social Responsiveness Scale (SR5;

Table 3 Key facts of the M-CHAT

The M-CHAT is a quick and accurate screener to detect toddlers suspected of having ASD between the age of 18 and 24 months in primary health settings and widely used across countries. To make use of the M-CHAT appropriately, parents and primary care providers need to be familiar with typical social development in infancy and toddlerhood.

The screening opportunity is also an important chance to educate parents and help them to take care of their child more appropriately.

Screening positive children via the screen-rescreen procedure should be monitored regularly, and services should be provided that meet the individual child's and parents' needs even before diagnosis is finalized.

The purpose of the M-CHAT to detect children with ASD and provide intervention as early as possible will be successful when combined with community-based developmental surveillance.

Some parents are not concerned about their child's development even if the child is screen positive. In such cases, continuous developmental surveillance will be important so that support can be provided once they are ready to receive it.

The optimal age at first screening (whether it should be at 18 months or 24 months) has yet to be determined and requires the accumulation of more follow-up data from studies in different settings.

The M-CHAT items most sensitive to ASD are common to US, Chinese, and Japanese children in different contexts. These are declarative pointing (item 7), follows a point (15), brings to show (9), and pretend play (5).

Constantino and Gruber 2005), a quantitative autistic trait measure. The *SRS* is a 65-item questionnaire which can quantitatively assess autistic traits in children; higher *SRS* scores indicate higher degrees of *social impairment*. As shown in Fig. 3, the parent-reported *SRS* scores were distributed widely and continuously in both the general population and ASD samples. The *SRS* score which fell in the range of ASD cut off approximately 2.5 % of the study population distribution, which was similar to the prevalence reported in a recent study in Korea (Kim et al. 2011).

Although there is an overlap between the general population and *ASD* samples and behavioral traits seemingly continue in the *ASD* sample, it remains unclear whether the underlying *neurobiological* structure and function are different or continuous on the spectrum. Given that there are many undiagnosed children with unmet needs (Kim et al. 2011), a dimensional approach using a quantitative measure such as the *SRS* could help to screen and identify those children in need in primary health settings or at school.

Conclusion

Early behavioral markers of *ASD* can reliably identify children as young as 18 months. Although parents who are concerned about their child may well have access to *early intervention* services with minimal or no delays, not all parents will be concerned by these early signs in such young children. Consequently, screening all children in primary health settings may be a practical and promising way to augment existing community developmental surveillance. Although autism screening should be modified according to the context of the community in which it is to

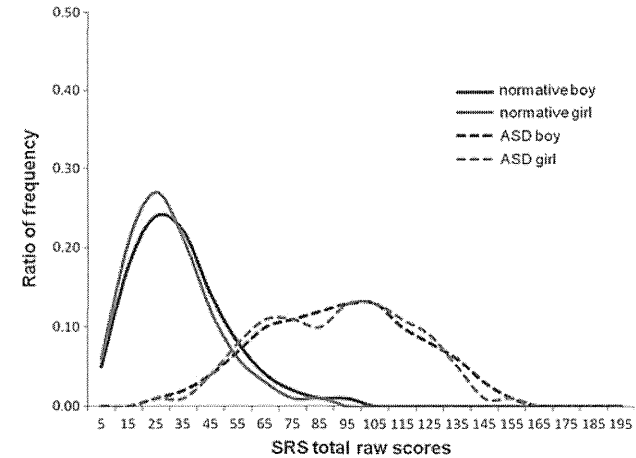


Fig. 3 Distribution of the Social Responsiveness Score (*SRS*) total raw scores in the general child population and in children diagnosed with autistic spectrum disorders (*ASD*) in Japan. The graph shows a continuous distribution of *SRS* scores. The *SRS* is a 65-item questionnaire which can quantitatively assess autistic traits in children. Normative data was obtained from 11,455 boys and 11,074 girls aged 7.15 years in mainstream classes nationwide. The *ASD* sample data (mean age: 10 ± 3.9 years, 78 boys, 79 girls) was obtained from child psychiatric clinics.

be applied, a combined strategy of using autism-specific screeners within routine health screening and utilizing existing resources should be cost-effective. With a substantial number of schoolchildren with *HFASD* remaining undiagnosed, age-appropriate screening using a *quantitative trait* measure should help to identify those with clinical needs. Moreover, heightened awareness among health and educational professionals as well as the public of *autistic behaviors* that are observable in toddlers and children will help to improve the *quality of life* of children with *ASD* and their families.

Key Terms

Early diagnosis of autism spectrum disorder (ASD). Diagnosis of *ASD* used not to be reliable under 3 years of age. However, based on accumulated data on the early signs of *ASD*, early diagnosis at age 2 made using standardized assessment tools has high stability. A relatively long time is needed (at least 1 h) to complete the diagnostic process.

Early detection of ASD. Identifying those children who will be diagnosed as having ASD by using a quick and accurate screening tool. The aim is to shorten any delay in diagnosis of ASD and provide appropriate intervention services as early as possible.

Early intervention. Clinically appropriate intervention for a child with ASD should be integrated and eclectic, and designed according to individual needs. Although intervention approaches vary from behavioral to pharmacological ones, the predominant approach for very young children with ASD is behavioral. Currently, there is little evidence to support one specific intervention program being superior to another. However, early intervention is, in general, one factor that would likely make a difference in the quality of life of children with ASD and their families both over the short term and long term.

Parental concern. Parents may have concerns about their child's development, when at around 2 years of age their child does not speak, does not respond to his/her name, does not follow simple commands, or always plays alone. When children are developmentally delayed, parents are likely to be aware of language delay in their child with ASD. When children have average or superior IQ, parents may not have concerns about social abnormalities their child shows. A lack of parental concern is likely to delay diagnosis and thus access to intervention.

Joint attention behavior. Responsive *joint attention* behaviors such as *following a point* (the child looks to where the mother is pointing) and *following a gaze* (the child looks to where the mother is looking) emerge in infants at around 10 months of age. Gradually infants become able to spontaneously initiate *declarative pointing* (the child comments on objects pointed to, tries to share comments with the mother) and *bringing to show* (child demonstrates something he/she is interested in to the mother) by 18 months of age. A lack of or reduced joint attention alongside of *pretend play* is a red flag for ASD diagnosis.

Summary Points

- This chapter focuses on early identification of toddlers and children with autism spectrum disorder (ASD) in primary settings.
- Delay in diagnosis of ASD delays access to *early intervention*. Early intervention benefits children with ASD and their families by improving adaptive function and quality of life.
- Early behavioral markers of ASD can be reliably identified in children as young as 18 months, but parents do not necessarily have concerns about their child in regard to such markers.
- Recently, various autism *screening tools* applicable to children under 24 months of age have been developed. Some are designed for primary health settings and others are designed for more specialized clinical settings.
- However, most of the screening tools designed for primary health settings (level-one screeners developed specifically for the early identification of ASD in an

unselected or low-risk population and to be used by primary health professionals) require validation in total population follow-up studies.

- A cost-effective screening method is to screen all children in primary care settings by combining autism-specific screening with broad developmental screening and monitoring through the community developmental surveillance network.
- Screening items related to joint attention and pretend play are most sensitive to ASD in toddlerhood.
- Since a substantial number of children with high-functioning ASD are likely to be missed by autism screening in toddlerhood and remain undiagnosed, age-appropriate screening will help to identify those with clinical needs which become overt at school.
- It is necessary to heighten primary health and educational professionals' awareness of the early signs of ASD in order to provide support services which meet the clinical needs of children with ASD and their families.

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Quantitative autistic traits ascertained in a national survey of 22 529 Japanese schoolchildren

Kamio Y, Inada N, Moriwaki A, Kuroda M, Koyama T, Tsujii H, Kawakubo Y, Kuwabara H, Tsuchiya KJ, Uno Y, Constantino JN. Quantitative autistic traits ascertained in a national survey of 22 529 Japanese schoolchildren.

Objective: Recent epidemiologic studies worldwide have documented a rise in prevalence rates for autism spectrum disorders (ASD). Broadening of diagnostic criteria for ASD may be a major contributor to the rise in prevalence, particularly if superimposed on an underlying continuous distribution of autistic traits. This study sought to determine the nature of the population distribution of autistic traits using a quantitative trait measure in a large national population sample of children.

Method: The Japanese version of the Social Responsiveness Scale (SRS) was completed by parents on a nationally representative sample of 22 529 children, age 6–15.

Results: Social Responsiveness Scale scores exhibited a skewed normal distribution in the Japanese population with a single-factor structure and no significant relation to IQ within the normal intellectual range. There was no evidence of a natural 'cutoff' that would differentiate populations of categorically affected children from unaffected children.

Conclusion: This study provides evidence of the continuous nature of autistic symptoms measured by the SRS, a validated quantitative trait measure. The findings reveal how paradigms for diagnosis that rest on arbitrarily imposed categorical cutoffs can result in substantial variation in prevalence estimation, especially when measurements used for case assignment are not standardized for a given population.

Significant outcomes

- In a large Japanese child population, behaviorally measured autistic traits are continuously distributed without any apparent deflection in the distribution plot that would signal a natural cutoff for categorical diagnoses. This is similar to the distribution pattern in US and European samples.
- Autistic traits measured quantitatively by parents differ slightly by culture, suggesting the need to interpret autism spectrum disorder (ASD) severity ratings with the use of culturally calibrated norms.
- Many children who do not meet the diagnosis of ASD exhibit elevations in autistic traits measured quantitatively, suggesting the need to reconsider current diagnostic systems that assume discontinuity between affected and unaffected populations.

Limitations

- The response rate of this nationwide survey was 29%.
- There is a possibility of bias that would differentiate respondents vs. non-respondents.
- High-scoring children in the sample as a whole were not confirmed using diagnostic instruments, although quantitatively measured autistic traits were extensively clinically confirmed for a separate smaller sample.

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Key words: autism; questionnaire; prevalence; classification; diagnosis

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Introduction

Although to date the designation of pervasive developmental disorders in children – and the services to which affected children are entitled – rest on categorical case definitions, the concept of an autistic *spectrum*, along which the number and intensity of autistic features vary continuously from mild to severe, dates back to early epidemiological research by Wing and Gould (1). Wing (2) subsequently developed the concept of the autistic continuum, broadening the case designation beyond classic autism to encompass the mildest (but most prevalent) of the autism spectrum disorders (ASDs), pervasive developmental disorder not otherwise specified (PDD-NOS) assigned by diagnostic and statistical manual of mental disorders: text revision (DSM-IV-TR) (3). Several lines of subsequent research (4–7) now strongly suggest that the autism spectrum extends beyond this PDD-NOS subcategory to include subclinical levels of symptomatology, which are known to aggregate in the undiagnosed members of families with multiple-incidence autism. Very recently, Lord et al. (8) observed that diagnostic assignments of autistic disorder, Asperger's disorder, and PDD-NOS made by expert clinicians varied considerably across sites, despite the fact that distributions of scores on validated measures were similar. They concluded that current taxonomies should be revised to place priority on characterizing the dimensions of ASD while controlling for IQ and language level.

Clarifying the nature of the population distribution of autistic traits and symptoms across cultures has substantial implications for understanding a rise in prevalence over time (9) and for establishing the 'boundaries' of clinical affectation. A recent Korean study (10) suggested the highest ever reported prevalence for categorically defined ASD in a total population sample; in that study, symptom counts were found to be continuously distributed in the population.

Aims of the study

This study determined whether autistic traits would be continuously distributed in a population-based sample to establish the appropriate epidemiologic framework for interpreting the rise in estimated autism spectrum disorders prevalence over time.

Material and methods

Participants

The participants comprised a normative sample ($n = 22\ 529$) of schoolchildren, a child psychiatric

clinical sample ($n = 417$), and typically developing (TD) children ($n = 61$). The normative sample was exclusively assessed using the Japanese version of the Social Responsiveness Scale (SRS) (11). The latter two samples were more extensively assessed using standard diagnostic batteries for the purpose of validation and calibration of the Japanese version of the SRS.

In regard to the normative sample, questionnaires were distributed by mail to the caregivers of all students attending mainstream classes at primary or secondary schools in the 10 geographical areas making up Japan in 2010 ($n = 87\ 548$ caregivers). One hundred and forty-eight primary schools and 71 secondary schools participated in this study. All of them were community schools where >93% of children living in the community attend, according to the annual report of Japan's Ministry of Education, Culture, Sports, Science and Technology, 2010 (12). Questionnaires were returned for 25 779 children aged 6–15 years (response rate 29.4%). Questionnaires with missing answers were excluded so that all analysis was based on a complete data set, leaving a final normative sample of 22 529 participants (11 455 boys) with SRS data provided by their mothers ($n = 20\ 430$), fathers ($n = 1728$), both parents ($n = 166$), other caregivers ($n = 119$) or unspecified ($n = 86$). Each of the 9 grade levels comprised a minimum of 754 participants of each sex, and both sexes were proportionally represented (Table 1).

The clinical sample consisted of 257 children diagnosed with ASD (ASD group) and 157 children with psychiatric diagnoses other than ASD (non-ASD group) (Table 2). They were patients who visited one of 10 child psychiatric clinics dur-

Table 1. Social Responsiveness Scale total raw score distributions in the normative sample by sex and age (grade)

Grade	Sex						
	Males		Females		<i>t</i>	<i>P</i>	<i>d</i>
	N	Mean (SD)	N	Mean (SD)			
1	1655	37.3 (18.2)	1473	33.0 (16.7)	44.3	0.000	0.25
2	1521	36.2 (18.2)	1394	32.1 (16.3)	37.8	0.000	0.24
3	1384	35.4 (19.2)	1432	31.2 (16.4)	39.0	0.000	0.24
4	1375	33.7 (18.4)	1386	30.2 (16.3)	26.2	0.000	0.20
5	1449	33.0 (18.5)	1287	31.0 (17.5)	8.6	0.003	0.11
6	1203	31.9 (19.6)	1229	29.9 (17.8)	6.9	0.009	0.11
7	1072	32.3 (19.1)	1070	30.3 (17.8)	6.7	0.010	0.11
8	1007	32.7 (20.2)	1049	29.8 (18.2)	12.7	0.000	0.15
9	789	31.7 (20.7)	754	28.9 (18.6)	9.2	0.002	0.14
Total	11 455	34.1 (19.1)	11 074	30.9 (17.2)	13.4	0.000	0.18
Total children	22 529		32.5 (18.3)				

Grade 1 children are usually 6–7 years old. Most grade 1 participants were 7 years old at the time of the survey.

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ing 2008–2010 and whose caregivers gave informed consent to participate in this study. Their existing clinical diagnoses were confirmed according to DSM-IV-TR criteria (3) based on all of the clinical information available to our research team, which included experienced child psychiatrists and licensed clinical psychologists. Among the 257 children of the ASD group, 229 were subcategorized with 100% diagnostic agreement: 96 with autistic disorder, 65 with Asperger's disorder, 68 with PDD-NOS, and 28 were unspecified. Children in the non-ASD group were diagnosed with adjustment disorder, attention deficit hyperactivity disorder, anxiety disorder, eating disorder, schizophrenia, somatoform disorder, conduct disorder, mood disorder, or mental retardation. Moreover, 61 children recruited from local communities comprised a TD group and were confirmed in diagnostic interviews with the children and their parents to have no history of neuropsychiatric conditions.

The intellectual levels of the children in the clinical sample ranged from normal intelligence to severe mental retardation based on cognitive testing carried out at clinics [various versions of the Wechsler Intelligence Scale and the Revised Kyoto Scale of Psychological Development (13)] or educational/administrative records. The proportions of children with normal intelligence in the ASD and non-ASD groups were not significantly different ($\chi^2 = 1.42$, n.s.).

Measures

The social responsiveness scale. The SRS (11) is a 65-item questionnaire of autistic traits for use with 4- to 18-year-olds that can be completed in 15 min

Table 2. Comparison of Social Responsiveness Scale total raw score between the United States and Japan

Grade	Country							
	Japan		US		<i>t</i>	<i>P</i>	<i>d</i>	
	N	Mean (SD)	N	Mean (SD)				
1	3102	35.3 (17.6)	71	29.6 (25.6)	1.87	0.06	0.318	
2	2891	34.2 (17.4)	92	34.9 (26.9)	0.25	0.80	0.041	
3	2786	33.2 (18.0)	109	35.7 (26.8)	0.97	0.33	0.136	
4	2739	31.9 (17.5)	227	35.3 (24.9)	2.02	0.04	0.188	
5	2703	32.0 (18.0)	214	34.5 (25.3)	1.42	0.16	0.134	
6	2408	30.8 (18.7)	211	31.7 (21.5)	0.59	0.56	0.049	
7	2123	31.3 (18.4)	161	31.1 (20.6)	0.12	0.90	0.008	
8	2040	31.1 (19.1)	137	31.9 (23.7)	0.39	0.70	0.040	
9	1532	30.2 (19.7)	124	38.9 (29.2)	3.26	0.00	0.422	
Total	22 344	32.5 (18.2)	1626*	33.6 (24.7)	1.76	0.08	0.051	

Grade 1 children are usually 6–7 years old. Most grade 1 participants were 7 years old at the time of the survey.

*US data were cited from the SRS manual (p. 28) (11).

by any adult who has observed the child over time in naturalistic social settings. The SRS was developed to assess autistic symptoms or quantitative traits and has subsequently undergone extensive validation in US samples for use in subclinical and clinical child populations (4, 14–17) as well as in general child populations for behavioral genetic research (18–20). It also demonstrated satisfactory internal consistency (Cronbach's $\alpha > 0.95$), interrater reliability between parents and teachers ($r = 0.78$, $P < 0.01$), and concurrent validity with an interview-based instrument (21) ($r = 0.86$, $P < 0.05$ for preschoolers; $r = 0.48$, $P < 0.05$ for children aged 7–12; $r = 0.77$, $P < 0.001$ for adolescents aged 13–18) for Japanese children (22, 23) and also for German children (24). The Japanese version was used in this study. Higher scores on the SRS indicate higher degrees of social impairment. The 65 SRS items were further categorized into five treatment subscales (social awareness, social cognition, social communication, social motivation, autistic mannerisms) (11). The SRS total scores are generally unrelated to IQ in the normal range and distinguish children with ASD from those with other types of psychopathology (16).

The autism diagnostic interview-revised. The Autism Diagnostic Interview-Revised (ADI-R) (25) is a parent-report interview and is a research standard for establishing a diagnosis of autism. To meet the ADI-R criteria for autism, the cutoff must be reached in each domain of reciprocal social interaction, communication, and restricted, repetitive, and stereotyped patterns of behavior. The Japanese version of the ADI-R was used in this study, which has demonstrated good reliability and validity for Japanese children (26).

Ethical issues

The study protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan. Written informed consent to participate was obtained from the caregivers of each child participant.

Data analysis

Following examination of the SRS distribution as a function of age and sex, a cross-cultural comparison of SRS total scores provided by parents was performed between previously reported US norms (the SRS manual, p. 28) (11) and the obtained Japanese scores using *t*-tests. Factor analysis was performed using principal components analysis

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(PCA) on children in the ASD, non-ASD, and TD groups, and the most parsimonious model was subsequently examined by confirmatory factor analysis (CFA) in the normative sample. To address discriminant validity, comparisons of the SRS scores across diagnostic groups were made using analysis of variance (ANOVA) methods with Bonferroni correction whenever appropriate. Intraclass correlation coefficient (ICC) was computed for associations between SRS scores, full scale IQ, and ADI-R algorithm scores. In addition, a receiver operating characteristics (ROC) analysis was conducted to determine the cutoff points for primary and secondary screening; for the former, the cutoff point was where the sum of sensitivity and specificity was the largest, and for the latter, it was where the likelihood was the largest for children in the ASD, non-ASD, and TD groups, for boys and girls separately. Analysis was performed using SPSS 18.0J for Windows (SPSS Japan Inc., Tokyo, Japan), with AMOS 17.0J for Windows (SPSS Japan Inc., Tokyo, Japan) used for the confirmatory factor analysis.

Results

Population distribution

Social Responsiveness Scale score distribution among 6- to 15-year-old children in the Japanese general population is shown in Fig. 1, and mean SRS total raw scores by age group are presented for boy and girl subsamples in Table 1. To investigate the effects of age (grade) and sex on SRS scores, a 2-way ANOVA (grade \times sex) was conducted on the total raw scores. The interaction was significant ($F_{8,180,224} = 2.00$, $P < 0.05$, $\eta^2 = 0.00$), and the main effects of grade ($F_{8,180,224} = 20.03$, $P < 0.001$, $\eta^2 = 0.01$) and sex ($F_{8,180,224} = 157.37$, $P < 0.001$, $\eta^2 = 0.01$) were significant, although the effect size indicates that the differences in the SRS scores by grade and sex were modest.

Mean SRS score of each age group was within 0.2 standard deviations of the entire sample means for boys and girls respectively (boys 30.3–37.9, girls 27.5–34.3). Boys scored higher than girls across the entire age range, with the maximum sex difference seen for the youngest subgroup at grade 1 ($t = 44.24$, $P < 0.001$, $d = 0.25$). Therefore, we standardized the Japanese version of the SRS on each of the boy and girl subsamples across the age range (27).

Table 2 shows our Japanese normative data together with the original US parent and teacher rating data (the SRS manual, p. 28) (11) derived

from five different studies. Japanese children scored similarly to their US counterparts, except those in grades 4 and 9; here, Japanese children had significantly lower mean SRS scores than their US counterparts.

Factor structure. PCA suggested a one-factor solution for the 475 children comprising the clinical and TD groups (Table 3). Seven items (items 24, 29, 35, 37, 44, 49, 51) with factor loadings > 0.600 represented all three of the DSM-IV-TR criterion domains for autism. When 22 items with factor loadings < 0.400 were excluded, the first factor explained 34.8% of variance in SRS scores in this sample, consistent with the original US and German data for child psychiatric patients. When performed with the mean scores of the five treatment subscales, rather than the mean scores of 65 items, PCA gave a one-factor solution accounting for 77.2% in this sample.

Next, the single-factor model suggested by PCA and by extensive prior research on the SRS (20, 24) was subjected to CFA using data from the normative sample. The comparative fit index, the goodness of fit index, the adjusted goodness of fit index, and root mean square error of approximation were 0.677, 0.739, 0.722, and 0.055 for all 65 items, 0.811, 0.854, 0.840, and 0.055 for 43 items with factor loadings > 0.400 derived from PCA on the exploratory set, and 0.989, 0.987, 0.962, and 0.083 for the five treatment subscales. These findings lend support to the notion of a unitary factor influencing the multiple aspects of dysfunction that characterize autistic symptomatology in children in the general population.

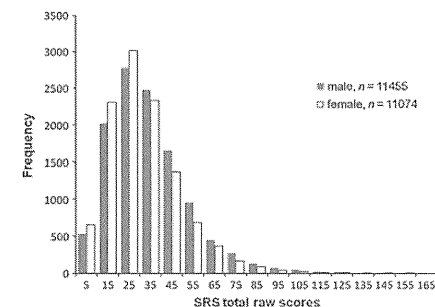


Fig. 1. Distribution of Social Responsiveness Scale (SRS) total raw scores rated by caregivers in the general sample of 6- to 15-year-old children.

Table 3. Principal components analysis of social responsiveness scale data

Component	ASD, non-ASD, and TD groups (n = 475)		
	Total	% of variance	Cumulative%
1	18.928	29.120	29.120
2	3.851	5.925	35.045
3	3.152	4.850	39.895
4	1.926	2.963	42.858
5	1.701	2.616	45.474

ASD, autism spectrum disorders; TD, typical development.

The clinical sample consisted of participants with ASD (n = 257) and non-ASD (n = 157).

Other psychometric properties

Table 4 indicated that the mean SRS total score of the ASD group was significantly higher than that of the clinical non-ASD (boys $t = 4.87$, $P < 0.001$, $d = 0.65$, girls $t = 4.68$, $P < 0.001$, $d = 0.83$) and TD (boys $t = 11.73$, $P < 0.001$, $d = 2.29$, girls $t = 11.80$, $P < 0.001$, $d = 2.66$) groups. The differences in SRS score were not pronounced among the ASD subcategories: the score did not discriminate between Asperger's disorder and PDD-NOS for either sex, as previously reported (23). As shown in Fig. 2, the SRS scores of both ASD and non-ASD groups were distributed widely and with significant overlap with the general population distribution. Table 5 shows the raw score cutoffs for the 99th, 97.5th, 95th, and 90th percentile values by sex for our normative sample and the proportion of boys and girls with diagnosed ASD who fell within the respective percentile cutoffs. In general, a higher proportion of diagnosed females were at the more extreme percentile rankings in comparison with males.

Social Responsiveness Scale score did not correlate with IQ (ICC = -0.23, n.s.) for 118 participants with IQs > 70 for whom formal test data were available (ASD 46, non-ASD 11, TD 61), although the subgroup with mental retardation tended to score higher. With regard to autistic symptoms, SRS score was significantly correlated with ADI-R total score (ICC = 0.66, $P < 0.001$; Fig. 3), as well as scores for the social interaction domain (ICC = 0.68, $P < 0.001$), communication domain (ICC = 0.58, $P < 0.001$), and restricted and repetitive behavior domain (ICC = 0.50, $P < 0.001$) for a subsample for whom data from both the SRS and ADI-R were available ($n = 36$; ASD 20, non-ASD 10, TD 6; mean age 8.0 years, range 4–18 years).

Receiver operating characteristics analysis informed two sets of cutoff points depending on the purpose of use. When used for primary screening of the general child population such as at

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school entrance, an optimal cutoff point was 53.5 for boys (sensitivity 0.91, specificity 0.48) and 52.5 for girls (sensitivity 0.89, specificity 0.41). For secondary screening of children referred to clinical settings, where a much higher rate of ASD is expected, the cutoff point of 109.5 for boys (sensitivity 0.23, specificity 0.96, likelihood ratio 6.14) and 102.5 for girls (sensitivity 0.32, specificity 0.95, likelihood ratio 5.73) increases the positive predictive value for ASD diagnosis up to 80.4% for boys and 79.2% for girls, given that the prevalence in Japanese child psychiatric clinics is 40%. Primary and secondary screening cutoffs correspond to a SRS T -score of 60 and 90 for boys and 62 and 92 for girls respectively.

Discussion

We conclude from these data involving a nationwide representative sample of schoolchildren that autistic traits measured by the Japanese version of the SRS are distributed continuously in the population; that the clinical validity of the measurements (in essence, their relevance to autism) appeared strong; and that the findings of this cross-cultural study recapitulate and extend what has been observed in smaller epidemiologic studies of autistic traits in other countries.

The results of this study of quantitative autistic traits – the largest of its kind – add substantial evidence in support of the continuous nature of autistic traits in the general population. This does not mean that individual cases of autism are never discretely or categorically determined. It has long been known, for example, that there exist categorical, relatively rare causes of autistic syndromes (e.g., fragile X syndrome, Rett syndrome, and tuberous sclerosis) caused by single gene abnormalities. The notion of an autistic continuum remains consistent with the existence of such discrete entities. The same is true for mild to moderate intellectual disability, which constitutes the extreme end of a normal distribution (the so-called "bell curve") but comprises a number of discrete syndromes (including but not limited to Down syndrome, Fragile X syndrome, etc.) in the severe end of the symptom distribution. Similarly, segments of the autistic continuum may be comprised of small clusters of discrete disorders (e.g., SHANK 1 mutations, 15q duplications, 16p11.2 deletions) that contribute to intervals at the pathological end of the distribution (for example 75–85, 90–110), but overlap in severity with other cases that represent quantitative accumulations of inherited liability transmitted by polygenic mechanisms or by gene–environment interactions. The causes of cases

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Table 4. Social Responsiveness Scale total raw score means of the ASD, non-ASD, and TD groups

	ASD subcategory						
	ASD	nonASD	TD	Autism	Asperger's disorder	PDD-NOS	Unspecified
M (Male/Female)	257 (203 : 54)	157 (78 : 79)	61 (30 : 31)	99 (77 : 19)	65 (46 : 17)	66 (54 : 14)	28 (24 : 4)
Age (years)							
Mean (SD) Range	10.0 (3.9) 4–18	12.1 (3.7) 4–18	9.61 (2.5) 6–18	9.0 (4.2) 4–18	10.7 (3.1) 4–17	10.0 (4.1) 4–18	11.68 (3.67) 6–17
Intellectual level (N)							
Normal	181	118	57	57	64	59	1
Boderline	14	9	4	8	1	3	2
Mild MR	10	12	0	5	0	3	2
Moderate MR	7	3	0	2	0	1	4
Severe MR	12	8	0	0	0	0	10
MR (unknown level)	33	7	0	22	0	2	9
SRS Mean (SD) Range							
Males	97.6 (27.4) 15–189†	69.7 (27.9) 13–141†	27.4 (16.6) 6–72†	88.5 (24.0) 46–139‡	82.4 (26.8) 15–132	78.4 (26.5) 24–144‡	
Females	86.1 (27.9) 21–153‡	62.1 (29.9) 12–134§	21.4 (16.2) 2–65§	91.4 (27.2) 21–133	91.0 (31.4) 36–153	74.7 (25.3) 40–114	
Total	87.3 (27.4) 15–189†	65.9 (29.1) 12–141¶	24.3 (16.5) 2–72¶	89.8 (24.5) 21–139**	84.6 (28.1) 15–153	77.7 (26.1) 24–144**	

SRS, Social Responsiveness Scale; ASD, autism spectrum disorders; TD, typical development; PDD-NOS, pervasive developmental disorder not otherwise specified; MR, mental retardation.

†ASD > non-ASD, TD ($t = 4.87$, $P < 0.001$, $d = 0.65$, $t = 11.73$, $P < 0.001$, $d = 2.28$, respectively); non-ASD > TD ($t = 7.75$, $P < 0.001$, $d = 1.67$).

‡Autism > PDD-NOS ($t = 2.48$, $P < 0.05$, $d = 0.44$).

§ASD > non-ASD, TD ($t = 4.68$, $P < 0.001$, $d = 0.83$; $t = 11.80$, $P < 0.001$, $d = 2.66$, respectively); non-ASD > TD ($t = 7.17$, $P < 0.001$, $d = 1.52$).

¶ASD > non-ASD, TD ($t = 7.53$, $P < 0.001$, $d = 0.76$; $t = 17.19$, $P < 0.001$, $d = 2.45$, respectively); non-ASD > TD ($t = 10.51$, $P < 0.001$, $d = 1.59$).

**Autism > PDD-NOS ($t = 3.05$, $P < 0.05$, $d = 0.49$).

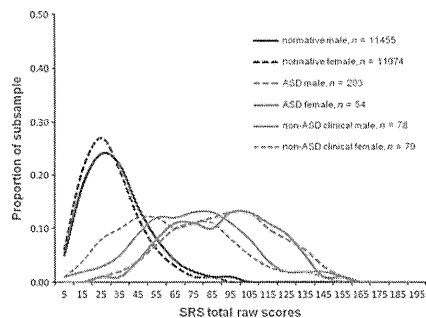


Fig. 2. Distribution of Social Responsiveness Scale (SRS) total raw scores in child psychiatric patients with and without autistic spectrum disorders (ASD).

Table 5. Proportion of children with autism spectrum disorders (ASD) corresponding to the 99th, 97.5th, 95th, and 90th percentile values among the ASD group of the Japanese clinical sample

Percentile value	Normative sample (n = 22 529)		ASD group (n = 257)			
	Raw score cutoff		N(%)			
	Males	Females	Males (n = 203)	Females (n = 54)		
≥ 99	98	87	70	34.5%	28	51.9%
≥ 97.5	81	73	117	57.6%	36	66.7%
≥ 95	70	63	147	72.4%	42	77.8%
≥ 90	58	53	173	85.2%	44	81.5%

represented by any given score in the distribution may be independent, partially overlapping, or fully overlapping with the underlying causes of other cases at the same level of severity. The result is a continuous distribution encompassing both discrete and quantitative pathways to affectation across a wide range of severity (28–32). We note that in a recent large general population twin study, Robinson et al. (33) demonstrated overlap in causal influence on autistic symptomatology at each of the first, second, and fifth percentiles of severity in the population.

In our study, there was no evidence of a natural cutoff that differentiated children categorically affected from those unaffected by ASD. The parent-report Japanese SRS cutoff scores for secondary screening derived from our ROC analysis, 109.5 for boys and 102.5 for girls, would comprise approximately 0.5% of our normative sample. On the other hand, the ASD primary screening cutoff with the highest sensitivity, 53.5 for boys and 52.5 for girls, encompassing 10.9% of our normative sample, identifies subthreshold conditions in

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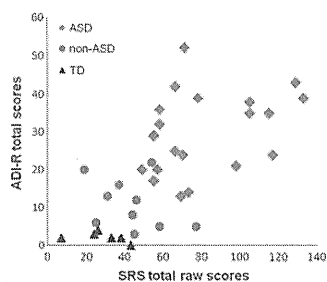


Fig. 3. Social Responsiveness Scale (SRS) total raw scores as a function of Autism Diagnostic Interview-Revised (ADI-R) total scores for children with autism spectrum disorders (ASD), non-ASD, and typical development (TD).

children that might warrant clinical attention (11). Taken together, these findings complement a recent Korean study (10), in which categorical screening and diagnostic confirmation revealed (and validated) what a continuous distribution of symptom counts. In our normative sample, a parent-report Japanese SRS raw score of 74 for boys and 80 for girls would cut off approximately 3.74%, 1.47% of each gender-specific population distribution, which is very near the prevalence for ASD reported in the Korean study (2.64%) (10).

Our observation of higher quantitative autistic trait scores in males than in females confirms across cultures a subtle but statistically robust gender difference (11, 18, 24). The sex distribution pattern has potentially profound implications for sex disparities universally observed at the extreme end of the distribution (i.e., in clinical ASD cases), where such disparities would be expected to be accentuated, as is true for any normally distributed trait such as height. The magnitude of the sex difference in our sample ($d = 0.18$) was smaller than that in the US data set (11) ($d = 0.37$) but similar to the German normative sample (24) ($d = 0.16$). Accentuation of the gender difference in the US data set could potentially relate to its being derived from a twin sample, given that male twins score higher than non-twins (34). Japanese children diagnosed with ASD were rated as having somewhat lower quantitative trait scores than their US and German counterparts. Such cross-cultural differences could be partly explained by cultural differences in responding to Likert-type rating, on which Japanese informants have a higher tendency to use the midpoint on the scales and US informants a higher tendency to use the extreme values (35).

The results of the exploratory factor analysis for the clinical sample replicate those of previous

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studies (17, 18), and the results of the confirmatory factor analysis for a very large general population underscore the presence of a primary underlying factor that influences the symptoms representing all three DSM-IV-TR criterion domains of autism. Factor structure has important implications for understanding the core neuropsychological mechanisms underlying autistic traits and symptoms, which are relevant to not only the pursuit of biomarkers and genetic susceptibility factors related to ASD but also diagnostic paradigms (20, 31).

There are two major limitations in this study. First, the response rate was low (29%), although it is keeping with what is expected from population-based surveys. Second, high-scoring children in 22 529 Japanese schoolchildren were not confirmed using any diagnostic instruments, although quantitatively measured autistic traits were extensively clinically confirmed for the separate smaller sample.

In the present study, although the instrument capably distinguished children diagnosed with ASD from children diagnosed with other psychiatric conditions, the score distribution for both clinical groups overlapped. A possible interpretation of this observation, given that autistic traits exhibit considerable independence in causation from many forms of psychopathology in genetic epidemiologic research (15, 36), is that autistic traits, when present, exacerbate other types of psychopathology when they cooccur with autistic traits as comorbid conditions. For some neurodevelopmental conditions, however, it has also become increasingly clear that there are elements of genetic causation that genuinely overlap with the genetic cause of autism; these include ADHD, tic disorders, and developmental coordination disorders, among others (37).

In conclusion, our study provides strong evidence of the continuous nature of autistic symptomatology in the general population, as has been reported in previous studies (1, 18, 19, 37). The findings underscore the notion that paradigms for categorical case assignment are superimposed on a continuous distribution, which can result in substantial variation in prevalence estimation, especially when the measurements used in case assignment are not standardized for a given population (i.e. by gender, informant, culture, etc.). In other words, these data illustrate that when imposing an arbitrary, non-standardized cutoff for diagnosis, small, clinically insignificant changes in the cutoff value can result in significant changes in prevalence, especially when operating at the steeper slopes of the distribution. Our results support the importance, validity, and feasibility of determining standardized quantitative ratings of autistic

traits and symptoms across cultures, the implementation of which has the potential to advance international collaborative research on autism and related conditions. Finally, these results call for a rational approach to revising systems of diagnosis and service delivery that currently perpetuate the notion of discontinuity between ASD-affected and unaffected populations.

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Declaration of interest

Dr. Constantino receives royalties for commercial distribution of the SRS, which is published by Western Psychological Services. No royalties were generated from use of the scale for this research study, and the study was exclusively designed to address scientific questions in the domains of epidemiology and public health.

The authors have no conflict of interests to declare with respect to this article.

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Clinical Study

Utility of Teacher-Report Assessments of Autistic Severity in Japanese School Children

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Recent studies suggest that many children with milder autism spectrum disorder (ASD) are undiagnosed, untreated, and being educated in mainstream classes without support and that school teachers might be the best persons to identify a child's social deviance. At present, only a few screening measures using teacher ratings of ASD have been validated. The aim of this study was to examine the utility of teacher ratings on the Social Responsiveness Scale (SRS), a quantitative measure of ASD. We recruited 130 participants aged 4 to 17 years from local schools or local pediatric outpatient clinics specializing in neurodevelopmental disorders that included 70 children with ASD. We found that the teacher-report SRS can be reliably and validly applied to children as a screening tool or for other research purposes, and it also has cross-cultural comparability. Although parent-teacher agreement was satisfactory overall, a discrepancy existed for children with ASD, especially for girls with ASD. To improve sensitivity in children at higher risk, especially girls, we cannot overstate the importance of using standardized norms specific to gender, informant, and culture.

1. Introduction

The current professional consensus is that early diagnosis and subsequent early treatment of autism spectrum disorder (ASD) can facilitate development and learning [1, 2], reduce the need for treatment later in life [3, 4], and improve long-term prognosis in adulthood [5, 6]. However, not all families with children with ASD necessarily get timely access to treatment and other support. Delayed identification and diagnosis of ASD have been associated with subtypes of ASD [7–10], cognitive level [10, 11], gender [11, 12], and demographic factors such as low socioeconomic status [8, 10]. Diagnosis of ASD tends to be delayed in children having both milder autistic symptoms and above-average general cognitive ability, especially in girls. For example, reported age at first diagnosis of Asperger, syndrome ranges from 7 to 11 years [9, 10, 12, 13]. In a Japanese nationwide survey of adults with high-functioning ASD, the median age at first diagnosis was 10.3 years [6].

Recent epidemiological studies [14, 15] have revealed that most mainstreamed children with ASD were undiagnosed

and untreated. Although most of these children might have had few diagnosable symptoms during preschool to draw the attention of primary health professionals, school teachers should be the best persons to identify any overt social deviance [16, 17].

At present, many quantitative behavioral measures of ASD have been created and validated in both primary care and clinical settings. However, these measures were largely validated for use by parents, not teachers, except in the case of the Autism Spectrum Screening Questionnaire (ASSQ), the Social Communication Questionnaire (SCQ), and the Social Responsiveness Scale (SRS). The ASSQ is a 27-item questionnaire that was originally developed as a first-stage population screening instrument in a prevalence study of Asperger, syndrome in mainstream schools with teachers as target raters [18], and it has been validated as a general population screen [19, 20]. The reliability and validity of both parent and teacher ASSQ ratings in a clinical setting have also been reported, although parent-teacher agreement was low to moderate for children with high-functioning ASD [21]. The SCQ [22] is a 40-item screening instrument that has been

investigated mainly as a parent-report screen. In one study of children with ASD and their siblings [17], the teacher-report SCQ-Current version was moderately correlated with the parent-report SCQ-Lifetime version, whereas it was strongly correlated with the teacher-report SRS. The SRS was developed as a quantitative measure of autistic traits in children [23], and the parent-report SRS has been extensively validated for the general child population [24–27] as well as for clinical samples [24, 28–32] not only in the USA but also in Europe, South America, and Asia. On the other hand, the literature on the utility of the SRS as a screening tool assessed by teachers is still limited [17, 31, 33]. Constantino et al. [34] demonstrated that the teacher-report SRS exhibited strong correlations with the parent-report SRS ($r = 0.72$), and the combined use of both parent and teacher reports resulted in extremely high sensitivity and specificity for a diagnosis of ASD in 271 children with ASD and 171 children without ASD, including 52 child psychiatric patients and 119 unaffected siblings. Schandling et al. [17] examined the utility of parent- and teacher-report SCQ and SRS in 1,663 children with ASD and 1,712 unaffected siblings from 1,655 families and showed that the screening properties of the teacher-report SRS were superior to those of the teacher-report SCQ-Current. In their study, the teacher-report SRS was more congruent with clinician-observed behaviors than with parent-reported behaviors and raised the possibility that behaviors exhibited by the children with ASD are contextually related and might be more congruent across classroom and clinical settings [17]. Fombonne et al. [31] examined the psychometric properties of the SRS-Spanish version in a Mexican sample consisting of 140 children with ASD and 319 community controls and found that the teacher-report SRS was an excellent screening tool similar to the parent-report SRS. In addition, they noted that the parent-teacher correlation of the SRS was much higher in the ASD sample compared with the control group.

Although some evidence exists on the SRS as a screening tool assessed by teachers, its utility has not been examined in an Asian population. Further, the reason for the discrepancy between parent and teacher reports on this scale is unclear.

Thus, the main aim of this study was to examine the utility of the SRS-Japanese version as a teacher-report screening tool for ASD. To this end, we examined test-retest reliability and discriminant/convergent validity of the teacher-report SRS, parent-teacher correlations or discrepancies on the SRS, and screening cutoffs in Japanese children aged 4 to 17 years.

2. Materials and Methods

2.1. Participants. This study involved 130 children consisting of 70 children with ASD (51 boys, mean age 8.6 [3.7], range 4–17 years) and 60 children without ASD (39 boys, mean age 8.0 [2.5], range 5–15 years; 24 with any neuropsychiatric diagnosis other than ASD; and 36 typically developing [TD] children). Seventy-eight children (23 with ASD, 19 with any neuropsychiatric diagnosis, and 36 with TD) currently participated in our ongoing community-based longitudinal study of child mental health at the National Center of Neurology

and Psychiatry (NCNP), Japan. All research participants were attending mainstream classes at local schools. We also recruited 20 children from a local special school for children with learning disabilities (15 with mental retardation [MR] and ASD, 5 with MR only). In addition, we recruited 32 patients diagnosed with ASD from three local pediatric outpatient clinics specializing in neurodevelopmental disorders.

The gender ratio did not significantly differ between children with ASD and those without ASD ($\chi^2 = 0.94$, ns). Mean age did not significantly differ between groups ($t = 1.16$, ns).

2.2. Measures

2.2.1. The Social Responsiveness Scale. The SRS is a 65-item questionnaire of autistic traits for use with 4–18-year-olds that can be completed in 15 minutes by parents or teachers who have observed the child over time in naturalistic social settings [23]. The SRS was developed to assess autistic symptoms or quantitative traits and has subsequently undergone extensive validation in general and clinical child populations in the USA and other countries. The 65 SRS items can be categorized into five subscales (social awareness, social cognition, social communication, social motivation, and autistic mannerisms). Each item is scored on a 4-point scale, and total score ranges from 0 to 195, with higher scores indicating higher degrees of social impairment. We used the teacher version in the present study and also the parent version as a subsample. The Japanese version of the parent SRS exhibited a skewed normal distribution in the general population with a single-factor structure, had no relation to IQ within the normal intellectual range [27], and demonstrated satisfactory discriminant and convergent validity [27, 35]. Both the parent- and teacher-report SRS were standardized on boys and girls separately [36].

2.2.2. The Autism Diagnostic Interview-Revised (ADI-R). The Autism Diagnostic Interview-Revised (ADI-R) [37] is a parent-report interview and a research standard for establishing a diagnosis of autism. The algorithm generates scores in each of three domains: reciprocal social interaction; communication; and restricted, repetitive, and stereotyped patterns of behavior. We used total scores of three domains of the Japanese version of the ADI-R [38] for the analysis in this study.

2.2.3. The Autism Diagnostic Observation Schedule (ADOS). The ADOS [39] is a semistructured behavioral assessment of social interaction, communication, and stereotyped behaviors. The algorithm generates scores in each of the three domains. We used total scores of the social and communication domains of the Japanese version of the ADOS [40] for the analysis in this study.

2.3. Procedure. The study protocol was approved by the Ethics Committee of the NCNP. A written informed consent was obtained from the parents of each child participant, and the study was conducted from 2010 to 2012.

First, parents were informed about the study by a letter from the investigators, which was distributed by the investigators themselves, a principal teacher, child psychiatrist, or pediatrician. Second, after providing the written consent, parents asked classroom teachers to complete the SRS on their children. Among all returned questionnaires, we excluded 16 teacher reports (11.0%) that had one or more missing answers, leaving 130 teacher reports on 130 children. Among these, we obtained 109 parent reports on 109 children (57 with ASD, 52 without ASD [19 clinical, 33 TD]).

Our research team conducted diagnostic interviews at the NCNP for 78 children, at the special school for 20 children, and at clinics for 32 children.

ASD diagnoses were confirmed according to DSM-IV-TR criteria based on all available clinical information by our research team that included experienced child psychiatrists and licensed clinical psychologists. To corroborate each ASD diagnosis, we evaluated the severity of autistic symptoms using either the Japanese versions of the Autism Diagnostic Interview-Revised (ADI-R) [38], the Autism Diagnostic Observation Schedule (ADOS) [40], the Diagnostic Interview for Social and Communication Disorders [41], or other semistructured interviews developed and validated in Japan [42]. Among 70 children with ASD, 55 were subcategorized with 100% diagnostic agreement based on available information among our research team: 24 with autistic disorder, 10 with Asperger's disorder, and 21 with pervasive developmental disorder, not otherwise specified. For 15 children, we reached complete agreement on a diagnosis of ASD, although we could not reach agreement on the subcategory.

The non-ASD diagnoses of 24 children were attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, specific phobia, social phobia, obsessive-compulsive disorder, enuresis, tic disorder, or mental retardation. These diagnoses were confirmed by diagnostic interviews with children and their parents using the Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime (K-SADS-PL), Japanese version. By parent interview, we confirmed the typical development of 36 children as having no history of neurological or psychiatric disorders.

We judged intellectual level based on cognitive testing (i.e., various versions of the Wechsler Intelligence Scale or other measures) for 115 children and educational/administrative records for 15 children. Intellectual level ranged from normal intelligence to severe MR (normal to borderline 105, mild MR 8, moderate MR 6, severe MR 4, and unknown MR 7). The proportion of children with normal intelligence did not significantly differ between children with ASD (53/70) and those without ASD (52/60) ($\chi^2 = 2.5$, ns).

2.4. Data Analysis. To address discriminant validity, we compared mean total and mean subscale SRS scores by gender between children with ASD ($n = 70$) and those without ASD ($n = 60$). To examine test-retest reliability, we calculated the intraclass correlation coefficient (ICC) for a subsample ($n = 23$). To examine convergent validity, we computed Pearson's correlation coefficients between the SRS and ADI-R, ADOS, or full scale IQ scores on three subsamples ($n = 49, 56, 115$).

To examine the teacher-parent discrepancy, we calculated ICC and compared mean total and mean subscale SRS scores by group (ASD versus non-ASD) and by gender using a paired t -test on a subsample ($n = 109$) that included both teacher and parent ratings. Finally, we conducted a receiver operating characteristics (ROC) analysis to compare the area under the curve (AUC) for the parent- and teacher-report SRS for a subsample ($n = 109$), and determined the cutoff scores that maximized sensitivity and specificity for the teacher-report SRS for the total sample.

All analysis was performed using SPSS 18.0J for Windows.

3. Results

3.1. Discriminant Validity. Table 1 presents the mean raw teacher-report SRS scores for the total sample ($N = 130$; ASD 70, non-ASD 60 [non-ASD diagnosis 24, TD 36]) by gender. Total scores and the five subscale scores were significantly higher in children with ASD than in those without ASD for both genders, except for social awareness and social motivation subscales in girls, where the mean subscale scores did not significantly differ between girls with ASD and those without ASD.

3.2. Test-Retest Reliability. Among 130 children, 23 (ASD 1, non-ASD diagnosis 3, TD 19) were assessed by their classroom teachers on two occasions with a mean interval of 40.0 days (12–131 days). Test-retest reliability was shown to be excellent for the total score (time 1: mean SRS 63.2 [22–103]; time 2: mean SRS 61.4 [24–119]; ICC = 0.87; $P < 0.001$).

3.3. Convergent Validity. SRS total score was significantly positively correlated with ADI-R total score ($r = 0.30$, $P < 0.05$) in a subsample with available data from both the SRS and ADI-R ($n = 56$, ASD 21, non-ASD diagnosis 14, TD 21; 36 boys) and also significantly correlated with ADOS total score ($r = 0.30$, $P < 0.05$) in a subsample with available data from both the SRS and ADOS ($n = 49$, ASD 20, non-ASD diagnosis 16, TD 13; 35 boys). In 115 children with available IQ data, the SRS score did not significantly correlate with IQ ($r = -0.14$) for 97 children with IQs ≥ 70 (ASD 46, non-ASD diagnosis 16, TD 35; 66 boys), whereas it significantly correlated with IQ in 18 children with IQs < 70 (ASD 11, non-ASD diagnosis 7) ($r = -0.58$, $P < 0.05$).

3.4. Parent-Teacher Correlation and Discrepancy. Among 130 total participants, 109 participants (ASD 57, non-ASD 52, including non-ASD diagnosis 19 and TD 33) were rated by both their teachers and parents at almost the same time (Table 2). For this subsample (73 boys, mean age 10.9 [2.8], range 7–14 years), ICCs showed moderate to large agreement between teachers and parents for all 109 children (73 boys and 36 girls; ICCs = 0.48, 0.50, and 0.40, resp.; Table 3). Among five subscales, ICCs ranged from moderate to large (ICCs = 0.29–0.53, P values < 0.05), except for the social awareness subscale in girls (ICC = 0.08, ns).

Table 4 shows that children with ASD of either gender were rated significantly higher by parents than by teachers on

TABLE 1: Mean raw SRS scores of teacher ratings of children with ASD and without ASD ($N = 130$).

Subscale	Boys ($n = 90$)			Girls ($n = 40$)		
	ASD ($n = 51$) M (SD)	Non-ASD ($n = 39$) M (SD)	t	ASD ($n = 19$) M (SD)	Non-ASD ($n = 21$) M (SD)	t
Awareness	11.6 (0.5)	7.4 (3.6)	4.8 ^a	8.7 (3.9)	7.1 (4.3)	1.3 ^d
Cognition	14.8 (6.2)	9.3 (6.0)	4.2 ^a	12.6 (4.9)	7.3 (5.3)	3.3 ^b
Communication	27.3 (10.2)	16.8 (10.0)	4.9 ^a	24.7 (12.7)	13.1 (10.7)	3.1 ^b
Motivation	11.0 (5.2)	8.4 (5.7)	2.2 ^c	10.8 (5.2)	8.4 (6.0)	1.4 ^d
Mannerisms	13.9 (8.5)	7.2 (5.4)	4.5 ^a	11.3 (8.4)	5.5 (6.4)	2.5 ^c
Total	78.6 (29.9)	49.1 (26.9)	4.8 ^a	68.2 (28.8)	41.5 (30.2)	2.9 ^a

Note. SRS: Social Responsiveness Scale; ASD: autism spectrum disorder.

^a $P < 0.001$. ^b $P < 0.01$. ^c $P < 0.05$. ^d ns.

TABLE 2: Demographic characteristics of 109 children rated by both teacher and parent.

	ASD ($n = 57$)	Non-ASD ($n = 52$)	
		Neuropsychiatric diagnosis ($n = 19$)	TD ($n = 33$)
Boy: girl	41:16	12:7	20:13
Age (years)			
Mean (SD), range	8.60 (3.90), 4–17	8.26 (2.77) 5–15	7.67 (2.13) 5–12
Intellectual level (n)			
Normal	34	9	33
Borderline	14	5	0
Mild MR	3	4	0
Moderate MR	2	0	0
Severe MR	2	1	0
MR (unknown level)	2	0	0
IQ*	$n = 49$	$n = 19$	$n = 32$
Mean (SD), range	91.2 (26.8), 31–148	82.7 (23.3), 27–113	109.7 (13.8), 85–146

Note. Between the ASD and non-ASD groups, no significant differences existed in gender ratio ($\chi^2 = 0.25$, ns) or age ($t = 1.2$, ns). The proportion of intellectual level did not differ significantly by group ($\chi^2 = 9.4$, ns). For 100 children with available IQ data, mean IQ did not significantly differ between groups (91.2 [26.8] for ASD, 99.7 [22.0] for non-ASD). Among the ASD and two non-ASD groups, no significant differences existed in gender ratio ($\chi^2 = 0.51$, ns) or age ($F = 0.84$, ns). The proportion of intellectual level differed significantly by group ($\chi^2 = 28.5$, $P < 0.005$). *For 100 children with available IQ data, mean IQ of the ASD group ($n = 49$) and that of the non-ASD neuropsychiatric diagnosis group ($n = 19$) were lower than that of the TD group ($n = 32$) ($t = 4.1, 4.6$, respectively, P values < 0.001), whereas no significant difference existed between the former two groups ($t = 1.2$, ns). MR: mental retardation; ASD: autism spectrum disorder; TD: typically developing.

the total scores. Among five subscales, significant differences in ratings between parents and teachers were found only for autistic mannerisms in boys with ASD, whereas subscale ratings on social cognition, social communication, and autistic mannerisms were significantly different in girls with ASD. On the other hand, children without ASD of either gender were rated similarly by parents and teachers on the total scale and on all subscales.

For children with ASD, we found a significant gender difference in teacher ratings on the SRS only on the social awareness subscale, where teachers rated girls significantly lower than boys ($t = 2.10$, $P < 0.05$). By contrast, we found no significant gender differences in parent ratings for this sample. On the other hand, for children without ASD, we observed no significant gender differences in both parent and teacher ratings (Table 4). That is, the gender difference was strongest in teacher reports on social awareness in the ASD group. Thus, teachers tended to rate boys and girls with ASD

lower compared to parents, and teachers tended to rate girls with ASD lower compared to boys with ASD.

3.5. ASD Cutoff Scores. ROC analyses of 109 children who were rated by both parents and teachers informed the AUC for each parent and teacher report on the SRS; among this sample, the teacher-report SRS accurately classified 73.2% of boys ($P < 0.005$) and 70.8% of girls ($P < 0.05$), whereas the parent-report SRS accurately classified 90.0% of boys ($P < 0.005$) and 94.8% of girls ($P < 0.005$) (Figures 1(a) and 1(b)). Therefore, the parent-report SRS appears to be more accurate than the teacher-report SRS as a screening tool. For the total sample, Youden's index was computed to determine the cutoff points that maximized the sum of sensitivity and specificity of the teacher-report SRS, 58.0 for boys (sensitivity 0.725, specificity 0.667, false-negative rate 0.275, false-positive rate 0.333, and positive likelihood ratio 2.177) and 43.0 for girls (sensitivity 0.789, specificity 0.667, false-negative rate 0.211,

TABLE 3: Intraclass correlation coefficients ($N = 109$).

Teacher rating	Parent rating					Total
	Awareness	Cognition	Communication	Motivation	Mannerisms	
Awareness	Total 0.38 ^a Boys 0.50 ^a Girls 0.08 ^d					
Cognition		Total 0.45 ^a Boys 0.46 ^a Girls 0.41 ^b				
Communication			Total 0.45 ^a Boys 0.45 ^a Girls 0.38 ^c			
Motivation				Total 0.48 ^a Boys 0.47 ^a Girls 0.53 ^a		
Mannerisms					Total 0.38 ^a Boys 0.38 ^a Girls 0.29 ^c	
Total						Total 0.48 ^a Boys 0.50 ^a Girls 0.40 ^b

Note. This subsample ($N = 109$) comprises 57 children with ASD and 52 children without ASD.

^a $P < 0.001$. ^b $P < 0.01$. ^c $P < 0.05$. ^dns.

TABLE 4: Mean raw SRS scores of parent and teacher ratings of children with ASD and without ASD ($N = 109$).

Rater	Boys ($n = 73$)		P	Girls ($n = 36$)		P
	Parent Mean (SD)	Teacher Mean (SD)		Parent Mean (SD)	Teacher Mean (SD)	
ASD ($n = 57$)		Boys ($n = 41$)			Girls ($n = 16$)	
Awareness	11.9 (3.4)	11.2 (4.3)	ns	10.2 (2.6)	8.6 (4.0)	ns
Cognition	16.2 (6.4)	14.2 (6.0)	ns	16.9 (4.8)	11.6 (4.7)	<0.005
Communication	30.4 (11.3)	26.6 (9.8)	=0.06	30.6 (9.2)	22.4 (12.0)	<0.05
Motivation	12.3 (5.8)	10.6 (5.3)	ns	12.5 (5.4)	10.8 (5.6)	ns
Mannerisms	16.4 (7.8)	12.7 (8.4)	<0.05	14.9 (7.4)	8.9 (6.5)	<0.05
Total	87.2 (31.3)	75.3 (29.2)	<0.05	85.1 (25.3)	62.3 (27.1)	<0.01
Non-ASD ($n = 52$)		Boys ($n = 32$)			Girls ($n = 20$)	
Awareness	6.6 (5.1)	7.4 (3.4)	ns	6.6 (3.3)	7.0 (4.4)	ns
Cognition	8.3 (4.4)	9.5 (6.0)	ns	6.6 (3.9)	7.5 (5.3)	ns
Communication	13.6 (7.0)	17.3 (10.2)	ns	10.8 (6.5)	13.7 (10.6)	ns
Motivation	7.3 (3.7)	8.7 (5.8)	ns	6.3 (4.9)	8.5 (6.1)	ns
Mannerisms	6.2 (4.5)	7.5 (5.5)	ns	4.2 (4.0)	5.8 (6.5)	ns
Total	42.0 (18.7)	50.5 (27.6)	ns	34.3 (19.9)	42.5 (30.6)	ns

Note. SRS: Social Responsiveness Scale; ASD: autism spectrum disorder.

false-positive rate 0.333, and positive likelihood ratio 2.369). These optimal cutoff scores were found to correspond to a T -score of 60 for each boy and girl according to T -score norms that were created for the Japanese standardization sample [36]. Because no natural cutoff was found that differentiated children diagnosed with ASD from those without ASD in the Japanese general and clinical samples for the parent-report SRS [27], these cutoff scores of teacher-report SRS

would identify many subthreshold conditions and at the same time miss many true-positive children. Compared to the previously reported optimal cutoff scores on the parent-report SRS (boys, sensitivity 0.91, specificity 0.48, and positive likelihood ratio 1.75; girls, sensitivity 0.89, specificity 0.41, and positive likelihood ratio 1.51) [27], the optimal cutoff scores on the teacher-report SRS would seem to result in a higher false-negative rate (boy, 0.28 versus 0.09, girl, 0.21 versus 0.11,

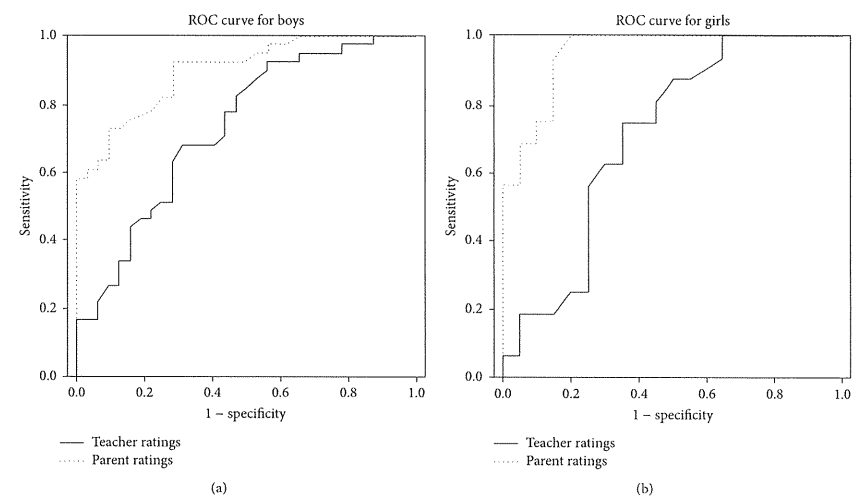


FIGURE 1: (a) Receiver operating characteristics (ROC) curve demonstrating sensitivity and specificity of both teacher and parent ratings for boys ($n = 73$). (b) Receiver operating characteristics (ROC) curve demonstrating sensitivity and specificity of both teacher and parent ratings for girls ($n = 36$).

teacher, and parent, resp.) and a lower false-positive rate (boy, 0.33 versus 0.52, girl, 0.33 versus 0.59, teacher, and parent, resp.). As addressed by Constantino et al. [34], when both parent and teacher rate a child as having a T -score of ≥ 60 , the positive likelihood ratio would improve up to 3.730 in our sample, which exceeds the teacher-report SRS alone or the parent-report SRS alone.

4. Discussion

The main aim of this study was to examine the utility of the teacher-report SRS as an ASD screening tool for Japanese children. In this study, the teacher-report SRS demonstrated excellent test-retest reliability and satisfactory discriminant and convergent validity for measuring autistic severity in children aged 4 to 17 years. Overall, there were moderate to large parent-teacher correlations on the total and subscale ratings. Thus, our findings showed that the teacher ratings on the Japanese version of the SRS can be reliably and validly applied to Japanese children at school or in clinical settings as a screening tool of ASD clinical settings.

Our results suggest overall good agreement on SRS measurements in terms of severity of autistic symptoms between teachers and parents; the correlations fall within the range reported in previous studies for the SRS (0.24–0.82) [17, 29–31, 33, 34, 43]. Our result is satisfactory compared to other psychiatric domains [43]. However, it is difficult to compare ours with the correlations reported by previous studies because of differences in sample size

(26–3375), the proportion of children with ASD included in the total sample (0–69.5%), and how control children were sampled (siblings from families who registered participation in autism research, community schools, and clinical non-ASD psychiatric patients); there appears to be no systematic tendency explaining the wide variation. For example, in Fombonne et al. [31], parent-teacher correlations for total SRS were stronger in children with ASD than in control children, but the opposite was found in Kanne et al. [43]. Based on data from Japan, the correlation for the non-ASD sample (Pearson's $r = 0.78$) [35] decreased to an ICC of 0.48 when calculated for the sample that included children with ASD (52.3%) in this study. Further studies are needed to answer this issue.

Despite overall good agreement, teachers tended to rate both boys and girls with ASD lower than did parents, although the teacher-parent discrepancy was not pronounced in children without ASD. Such discrepancy relating to the type of children (ASD versus non-ASD) was consistently found in previous studies [17, 34, 43, 44] except in a study based on a Mexican sample [31]. In the present study, teacher-parent discrepancy was pronounced, especially for girls with ASD (teacher 62.3 versus parent 85.1); parent ratings were significantly higher than teacher ratings not only on the total score but also on 3 (social cognition, social communication, and autistic mannerisms) of 5 subscales. One possible interpretation could be an effect of situational context as suggested by Sztatmari et al. [45] and Posserud et al. [19]. How children with ASD behave can change depending

on the situation, such as the degree of structurization, and it is likely that autistic behaviors of higher-functioning children with ASD are observed less often at school than at home if the school environment meets a child's needs. Shanding et al. [17] raised the possibility that teachers and clinicians similarly observe and report behaviors exhibited by children with ASD based on the stronger association between teacher ratings on the SRS and the ADOS compared to that between the teacher SRS and the ADI-R. Szatmari et al. [45] warned that this discrepancy between home and school might lead to higher parental stress. Thus, we should exercise caution when interpreting information from parents and teachers in diagnosis and assessment.

Regarding gender differences, it appears that teachers tend to rate girls with ASD lower than boys with ASD, whereas they rate girls without ASD higher than boys without ASD, although these differences reached statistical significance only on the social awareness subscale of the teacher report. Similar gender differences were reported in Norway for total population data using the ASSQ [19]. By contrast, in a Mexican sample [31], affected girls scored higher than affected boys on the teacher-report SRS, whereas control boys scored higher than control girls. However, closer inspection revealed a similar gender difference related to the social awareness subscale between ours and Fombonne et al. [31]. In both studies, teacher and parent ratings for girls did not agree on this subscale, and gender differences in teacher ratings were pronounced on this subscale. In this study, teacher ratings on this subscale also did not discriminate girls with ASD from those without ASD. The poor reliability and validity of this subscale might be related to the measurement of social awareness, which is not overt and is difficult to observe from the outside. Lai et al. [46] reported that women with ASD showed fewer autistic features than males but perceived themselves as having more autistic features, perhaps because they are better at hiding their autistic features, or perhaps because of greater self-awareness. Our finding of gender differences, if replicated, emphasizes the need for both a deeper understanding of gender differences in ASD and the establishment of a gender-specific norm.

The ROC analysis demonstrated that teacher ratings on the SRS classified both boys and girls with moderate accuracy, although the parent-report SRS appears to be more accurate than the teacher-report SRS as a screening tool. The optimal cutoff for boys was 58.0 in this study, which fell within the range of 51.5 to 64.5 proposed in previous studies of the teacher-report SRS [17, 31, 34, 44], whereas that for girls was 43.0 in our sample, which fell below the range. If this great discrepancy in cutoff scores between boys and girls is replicated in a different Japanese sample, the importance of establishing gender-specific norms for this population should be emphasized again. In this study, either sensitivity or specificity values were lower compared to those in studies that included only children with ASD and typically developing children [17, 31], which is consistent with studies that included children with non-ASD clinical conditions [34, 44]. Children with non-ASD psychiatric diagnoses such as ADHD or mood disorders tended to have

high SRS scores [47, 48], and there is an overlap in SRS scores of children with ASD and those of children with non-ASD psychiatric diagnoses [27]. That is, the sensitivity or specificity values in our sample might be associated with the type of non-ASD controls, including children with non-ASD psychiatric diagnoses whose mean SRS scores were expected to be higher than those of the normative sample.

Regarding cultural differences in teacher ratings of children with ASD, our female sample with ASD scored similar to children with ASD (86.5% male) in a large-sized study by Schanding et al. [17], whereas our male sample with ASD scored higher. However, our sample with ASD of either gender scored lower than children with ASD in other studies [31, 34]. This variance might be partly explained by the sampling method rather than culture-related differences, taking the heterogeneity of ASD into account. As for gender differences found in this study, little evidence exists, except that in a Mexican sample [31], to draw any conclusion about it from a cultural perspective. If our findings on gender differences are replicated in samples representing different cultures, we should consider culture-free gender differences. Or, if our findings are limited to a Japanese sample, we should consider any cultural factor such as social expectations of the female role in public settings, especially in terms of social awareness. Again, cross-cultural validity of the teacher-report SRS would be guaranteed if it is applied to children according to culturally calibrated gender-specific norms.

The major limitation of this study is its small sample size. Further, we did not use the same assessment battery to determine ASD status for children diagnosed with ASD. Comorbid psychiatric disorders were not assessed using diagnostic measures for 23 children with ASD. The strength of this study is that ASD was excluded for all of the non-ASD children.

5. Conclusions

In conclusion, this study provided evidence that the teacher-report SRS is a useful measurement of autistic severity with good reliability and validity and recapitulated what has been observed in studies conducted in other countries. Although parent-teacher agreement on the SRS was satisfactory, characteristic discrepancies specific to ASD diagnostic status and gender between informants should be kept in mind when interpreting the SRS from only one-sided informants. To improve sensitivity for children who are at higher risk, especially girls who are likely to remain undiagnosed, we emphasize the importance of combining information from multiple informants and using standardized norms specific to gender, informant, and culture for screening, clinical, or research purposes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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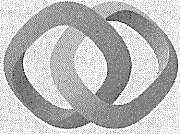
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STUDY PROTOCOL

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A cognitive-behavioral intervention for emotion regulation in adults with high-functioning autism spectrum disorders: study protocol for a randomized controlled trial

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Abstract

Background: Adults with high-functioning autism spectrum disorders (ASD) have difficulties in social communication; thus, these individuals have trouble understanding the mental states of others. Recent research also suggests that adults with ASD are unable to understand their own mental states, which could lead to difficulties in emotion-regulation. Some studies have reported the efficacy of cognitive-behavioral therapy (CBT) in improving emotion-regulation among children with ASD. The current study will investigate the efficacy of group-based CBT for adults with ASD.

Methods/Design: The study is a randomized, waitlist controlled, single-blinded trial. The participants will be 60 adults with ASD; 30 will be assigned to a CBT group and 30 to a waitlist control group. Primary outcome measures are the 20-item Toronto Alexithymia Scale, the Coping Inventory for Stressful Situations, the Motion Picture Mind-Reading task, and an ASD questionnaire. The secondary outcome measures are the Center for Epidemiological Studies Depression Scale, the World Health Organization Quality of Life Scale 26-item version, the Global Assessment of Functioning, State-trait Anxiety Inventory, Social Phobia and Anxiety Inventory, and Liebowitz Social Anxiety Scale. All will be administered during the pre- and post-intervention, and 12 week follow-up periods. The CBT group will receive group therapy over an 8 week period (one session per week) with each session lasting approximately 100 minutes. Group therapy will consist of four or five adults with ASD and two psychologists. We will be using visual materials for this program, mainly the Cognitive Affective Training kit.

Discussion: This trial will hopefully indicate the efficacy of group-based CBT for adults with high-functioning ASD.

Trial registration: This trial was registered in The University Hospital Medical Information Network Clinical Trials Registry No. UMIN000006236.

Keywords: Autism spectrum disorders, Emotion regulation, High-functioning adults, Cognitive-behavioral therapy, Randomized controlled trial

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Background

Autism spectrum disorders (ASD) are a group of developmental disorders that include qualitative impairment in interpersonal communication as a core symptom. Even for an adult with high-functioning ASD, whose intellectual development is within the normal range, it is difficult to overcome difficulties in understanding the thoughts and emotions of others; this leads to impairments in interpersonal communication [1-3]. In recent years, studies have shown that an individual may not only find it difficult to recognize the emotions of others but also struggle with identifying one's own emotions and matching the nature of those emotions with the appropriate strength and language given the current context; this can lead to difficulties in identifying or expressing their own mental states [4,5]. Some studies have shown that 50% of ASD adults have alexithymia, which is a personality construct characterized by a sub-clinical inability to identify and describe one's own emotions [6,7]. This inability to identify or express one's own mental states, coupled with a lack of emotion recognition, makes it even more difficult to establish mutual relationships. Failure to adapt to a group may become seriously affected and lead to interpersonal difficulties. Adults with ASD often present with one or more co-morbid disorders, such as anxiety or depression [8,9]. In many cases, a combination of mood disorders and anxiety arises due to chronic stress within a group. Hence, the treatment of patients with underlying ASD is a major issue for the mental health field. Even if symptomatic treatment is successful in relieving psychiatric symptoms, adults with ASD still find it difficult to adapt to society due to interpersonal communication difficulties. Recent research has also suggested that there are many adults with undiagnosed ASD among individuals who receive treatment for other psychiatric disorders. Many are diagnosed with ASD in adulthood without noticeable ASD symptoms during childhood [10].

Cognitive-behavioral therapy (CBT) interventions are being implemented within small group or individual therapy, with the aim of improving the regulation of emotions associated with ASD difficulties [11-15]. Sofronoff and colleagues [12] examined 71 children, aged 10 to 12 years, diagnosed with Asperger's syndrome (AS). In some cases, the children's parents were randomly assigned to one of three conditions (child-only intervention, child and parent intervention, and waitlist control). Small-group CBT was carried out, and the results for the three groups were compared among the three groups. Each of the intervention groups contained three participants, matched on sex and age. Two graduate student therapists conducted CBT for each group. There were 23 participants, over eight groups, in the child-only intervention group. Although there was no direct parental involvement, activities were

explained after the sessions, and parents were instructed to have their children perform tasks at home. There were 25 participants, over nine groups, in the child and parent intervention condition. The interventions for the children in this condition were the same as those in the child-only intervention condition, with one psychotherapist for each group, which also included two parents. Twenty-three individuals were assigned to the control group. Six 2 hour sessions, during which participants studied how to be emotionally aware and use appropriate methods for coping with emotions, were conducted over 1 week. Results were examined via children's self-assessments using the "James and the Maths Test", a story describing anxiety about a math test. The parents also completed an assessment using the Spence Child Anxiety Scale and Social Worries Questionnaire-Parent. These assessments were performed at pre- and post-intervention, and also during a follow-up session (6 weeks later). A significant intervention effect was observed when both children and parents took part in the intervention; the child-only intervention was the next most effective treatment. Furthermore, a randomized comparative trial conducted by Sofronoff and colleagues [13] revealed similar results for a small-group CBT intervention to help with anger control. Based on the efficacy of the emotion-regulation which these studies showed, the Cognitive Affective Training Kit (The Cat-kit) was developed [16]. It is designed to help individuals with ASD become aware of how their thoughts, feelings and actions all interact and, in the process of using the various visual components, they share their insights with others.

White and colleagues [17] developed a manual-based CBT program to target anxiety symptoms as well as social skill deficit in adolescents with ASD. Their treatment program includes 12 to 16 individual sessions of 50 to 75 minutes with session content tailored to the individual. Small-group CBT starts approximately 3 weeks after the start of the individual sessions. The small group sessions continue over five, 60 minute sessions, during alternate weeks. Parental participation during the intervention occurs for the last 10 to 20 minutes of their child's individual sessions. This treatment program was carried out with four children (aged 12 to 14 years) with ASD with a co-current anxiety disorder. The Child and Adolescent Symptom Inventory-20, a brief parent-report scale, was used to assess anxiety symptoms. The Anxiety Disorders Interview Schedule for Children/Parents, a clinician rating, was used to assess anxiety. The Social Responsiveness Scale was a parent-report scale that measures their child's social disability, and the self-reported Multidimensional Anxiety Scale for Children was completed by the children. All measures were administered at baseline, midpoint, endpoint, and 6 months following treatment. The treatment program was effective in

reducing anxiety in three of the four subjects and improving the social skills in all four subjects.

To our knowledge, the only detailed report on the efficacy of CBT intervention among adults with ASD comes from Cardaciotto and colleagues [11]. In this study, the subject was a 23-year-old male with AS and co-morbid social anxiety disorder. The intervention included individual CBT over 14 weeks; a clinician who did not administer the CBT examined the effects of the therapy. The subject was assessed at the initial examination (6 months before the intervention), 2 weeks before the intervention, immediately before the initial intervention, during the intervention, immediately after the intervention, and 2 months after the intervention, using the Social Phobia and Anxiety Inventory (SPAI), Liebowitz Social Anxiety Scale (LSAS), and Beck Depression Inventory II. The subject showed improvements across all three measures.

Objectives

The purpose of this study is to investigate the efficacy of group-based CBT for adults with ASD. Our primary hypothesis is that, through group-based CBT focusing on emotion-regulation and psychoeducation about ASD, adults with ASD can understand their own and others' emotions and thoughts, exercise emotion-regulation, and increase their knowledge of ASD and self-awareness, especially of their own strengths and weaknesses related to ASD. A small-group adult CBT study protocol will be prepared with reference to previous CBT studies. As noted above, parent training, as well as other forms of intervention, can be carried out along with a child's CBT.

Thus, parents gain a greater understanding of ASD and the necessary modifications to a child's environment, which is highly effective in enabling a parent being able to adapt to a child with ASD. However, unlike in children, adults with ASD need to understand more about their own strengths and weaknesses, as it is more desirable and practical that they are able to modify their own environment instead of his/her parents. Therefore, this study, which attempts to help improve social adaptation among adults with ASD, comprises two programs: (1) increasing the individual's emotional awareness and allowing them to acquire appropriate coping skills, and (2) increasing self-awareness through ASD psychoeducation, by learning about the symptoms and biological cause of ASD and the individual's strengths and weakness associated with it. These programs will be provided regularly, and the effects of these programs will be assessed.

Methods/Design

Trial design

This study is a randomized controlled trial. It follows a waitlist control, single-blinded (participants and psychologists who conduct the group-based CBT are not blinded and the assessors of all measures are blinded) design. The allocation of participants will be equal (1:1) across a CBT group (intervention group) and a waitlist control group. All assessment will be administered by the blinded assessors at the enrolment, post-intervention, and at 12 weeks follow-up. The entire trial design is illustrated in Figure 1. First, an assessment for eligibility will be performed. For individuals who meet the inclusion

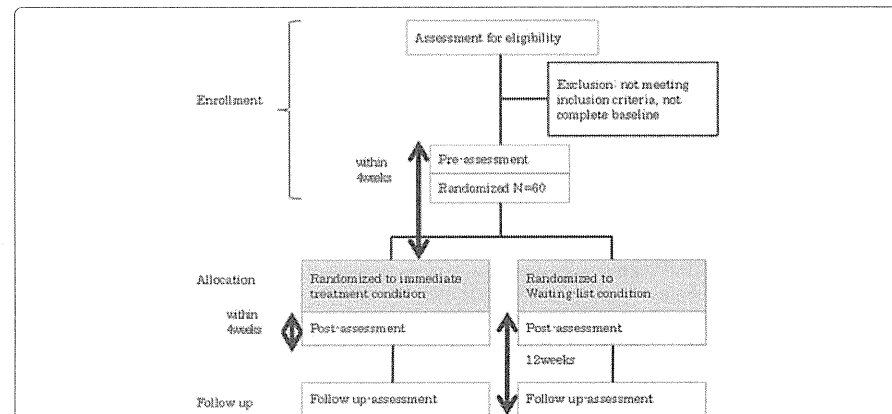


Figure 1 CONSORT flow chart of the clinical trial. The allocation of participants will be equal (1:1) across a cognitive-behavioral therapy group and a waitlist control group. All assessment will be administered at the enrollment, post-intervention, and at 12 weeks follow-up. Both pre- and post-assessment will be performed at 4 weeks before or after the treatment.

criteria, a pre-assessment will be performed no more than 4 weeks before the treatment. After pre-assessment, participants will be allocated into the immediate treatment condition or the waitlist condition. After the completion of treatment, post-assessment will be performed within 4 weeks. After an additional 12 weeks, a follow-up assessment will be performed. The pre-assessment and intervention will be conducted at the Department of Child and Adolescent Mental Health, the National Institute of Mental Health, National Center of Neurology and Psychiatry, and the Department of Child Psychiatry, the University of Tokyo Hospital. The allocation and post- and follow-up assessments will be conducted at the Department of Child Psychiatry, the University of Tokyo Hospital.

The target sample size is 60, and registration began on September 1, 2011. This trial was registered in the University Hospital Medical Information Network Clinical Trials Registry and approved by the International Committee of Medical Journal Editors (No. UMIN00006236).

Ethical consideration

The Ethics Committee of the National Institute of Neurology and Psychiatry (No. A2010-022) and Graduate School of Medicine and Faculty of Medicine at the University of Tokyo have approved the study protocol (No. 2702). All

participants will be asked to sign a written informed consent, as approved by the ethical committee of each site, according to the Declaration of Helsinki after receiving a complete explanation of the trial.

Participants

The participants will be individuals diagnosed with pervasive developmental disorder based on the text revision of the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV-TR) criteria [18]. In our study, the Cat-kit [16], which was used in the studies of Sofronoff and colleagues, will be used, along with the procedure of those studies. Sofronoff and colleagues had 23 to 25 participants in each of their intervention groups. Therefore we decided to use 25 participants each for the intervention and control groups, recruiting 30 individuals per group to account for potential dropouts.

The inclusion criteria are as follows: (1) age between 18 and 50 years; (2) a full intelligence quotient (IQ) of at least 85 and a verbal IQ of 100 or above (IQ will be evaluated using the Wechsler Adult Intelligence Scale, Third Edition [19]); (3) a specific diagnosis based on the Autism Diagnostic Schedule (ADOS) [20] or the Autism Diagnostic Interview, Revised (ADI-R) [21] with a score above the ASD cut-off; (4) high school graduate or above; (5) knowledge of one's diagnosis, (6) realization of one's poor

Table 1 All measures assessed at enrollment, pre-intervention, post-intervention, and follow-up, including primary and secondary outcomes

Measures	Time required (minutes)	Dx data	Pre-intervention	Post-intervention	Follow-up
DSM-IV-TR		o			
MINI	30		o		
WAIS-III	60	o			
AQ	10	o			
E-SQ	15	o			
ADI-R	(120: parent)	o			
ADOS	90	o			
SRS-A	15	o			
SCQ	(20: parent)	o			
MPMR	15		o	o	o
TAS-20	5		o	o	o
CISS	10		o	o	o
ASD	5		o	o	o
Questionnaire					
WHO-QOL26	10		o	o	o
GAF	30		o	o	o
STAI	10		o	o	o
SPAI	25		o	o	o
LSAS	10		o	o	o
CES-D	5		o	o	o

emotional self-awareness/ability to express emotion and poor understanding of others' emotions and thoughts, and (7) willingness to participate. Individuals with a comorbid psychiatric and/or unstable condition will be excluded (Table 1). The Mini-International Neuropsychiatric Interview [22] will be used to evaluate psychiatric comorbidity. Any individual who fails to attend more than three sessions will be regarded as 'dropping out', but supplementary instruction will be regarded as equivalent to attendance and will be offered up to three times. Current medication doses should not be increased greatly during the trial. Furthermore, current individual psychological therapy and regular medical treatment will be continued during the intervention. A detailed ASD assessment and diagnosis will be carried out for all intervention candidates. Recruitment of individuals with an ASD diagnosis will be conducted through the Department of Child Psychiatry or Neuropsychiatry at the University of Tokyo Hospital or an advertisement on the University of Tokyo Hospital web site.

Inclusion criteria

- Aged 18–50 years
- Primary diagnosis of autism spectrum disorders (based on criteria by psychiatrists from the text revision of the diagnostic and statistical manual of mental disorders, fourth edition)
- A full intelligence quotient of at least 85 and a verbal intelligence quotient of 100 or above
- Autism Diagnostic Schedule or Autism Diagnostic Interview, Revised score above the autism spectrum disorders cut-off point
- Educational qualifications: high school graduate or beyond
- Informed of his or her diagnosis
- Aware that he or she has poor emotional self-awareness or ability to express emotion and difficulty understanding others' emotions and thoughts
- Willing to participate in the study

Exclusion criteria

- A psychiatric comorbid and/or unstable condition

As shown in Table 1, candidates will be provided with a detailed diagnostic confirmation using the Autism-Spectrum Quotient, Japanese version [23], which is a self-report questionnaire measuring the degree to which any adult with a normal IQ possesses traits related to the autistic spectrum. Additional measures will include the Social Responsiveness Scale for Adults, Japanese version [24], which measures the severity of autism spectrum symptoms (completed by a relative), and the

Empathizing-Systemizing Quotient, Japanese version [25], which assesses a person's strength of interest in empathy (defined as the drive to identify with a person's thoughts and feelings and respond with an appropriate emotion). A person's strength of interest in systems is defined as the drive to analyze or construct a system. Additionally, interviews using the ADOS for individuals with ASD and interviews with parents using the ADI-R will be conducted. Final participation will be decided after confirmation that the subject meets participation criteria.

ADI-R, Autism Diagnostic Interview, Revised; ADOS, Autism Diagnostic Schedule; ASD, autism spectrum disorders; AQ, Autism-Spectrum Quotient; CES-D, Center for Epidemiological Studies Depression Scale; CISS, Coping Inventory for Stressful Situations; DSM-IV-TR, text revision of the diagnostic and statistical manual of mental disorders, fourth edition; Dx, Diagnosis; E-SQ, Empathizing-Systemizing Quotient; GAF, Global Assessment of Functioning; LSAS, Liebowitz Social Anxiety Scale; M.I.N.I., Mini-International Neuropsychiatric Interview; MPMR, Motion Picture Mind-Reading task; SCQ, Social Communication Questionnaire; SPAI, Social Phobia and Anxiety Inventory; SRS-A, Social responsiveness scale for adults; STAI, State-trait Anxiety Inventory; TAS-20, 20-item Toronto Alexithymia Scale; WAIS-III, Wechsler Adult Intelligence Scale- Third Edition; WHO-QOL 26, World Health Organization Quality of Life 26-item version.

Assessments/measures

Primary outcomes

Our hypothesis is that CBT will help adults with ASD to understand their own and others' emotions and thoughts and to exercise emotion regulation, by increasing their knowledge of ASD and self-awareness, especially their own strength and weakness related to ASD. Therefore, primary outcome measures will be the 20-item Toronto Alexithymia Scale, Japanese version (TAS-20) [26] scores at post-intervention to evaluate the ability to understand one's own mind and the percentage of correct response on the Motion Picture Mind-Reading task (MPMR) [27] at post-intervention to evaluate the ability of understanding the minds of others. As other primary outcome measures, we will also adopt the Coping Inventory for Stressful Situations, Japanese version (CISS) [28] scores at post-intervention to assess coping skills during stressful situations and the ASD questionnaire scores at post-intervention to assess the knowledge about ASD and the attitude for ASD. These measures are described in greater detail below.

The TAS-20 is one of the most commonly used measures of alexithymia. Alexithymia is characterized by a difficulty in identifying and describing emotions and the tendency to minimize emotional experience and focus

attention externally. This measure is a self-report one and consists of 20 items and three factors: difficulty in identifying feeling, difficulty in describing feeling, externally oriented thinking. Each item is rated from 1 (strongly disagree) to 5 (strongly agree) and the total score ranges from 20 to 100. The time required for this test is about 5 minutes.

The MPMR, developed by Wakabayashi and Katsumata [27], involves advanced theory of mind tasks. Tasks are based on the scenes from a television drama. A total of 41 video clips (each 3 to 11 seconds in length) are included from the television drama series, *Shiroyi Kyotō* [The White Tower], which depicts malpractice in a famous Japanese medical school. The participant is asked to judge whether the word or phrase presented on the screen aptly describes the person in each scene. The time required for this test is about 15 minutes.

The CISS determines the preferred coping style of an individual and assesses the relationship between the individual's coping style and his or her personality. Its results are useful for treatment and intervention planning. The CISS measures three types of coping styles: task-oriented, emotion-oriented, and avoidance coping. This measure is also based on self-reports. The CISS consists of 48 items and each item is rated from 1 (not at all) to 5 (very much). The total score of each of the three coping styles ranges from 16 to 80. The time required for this test is about 10 minutes.

The ASD questionnaire that assesses the knowledge about ASD and the attitude to ASD was developed for this study. The questionnaire involved 10 knowledge-based questions (1 = true to 3 = not true) and five attitude-based questions (1 = disagree to 5 = agree) regarding ASD. The time required for this test is about 5 minutes.

Secondary outcomes

We anticipate that they will experience improvement in anxiety and depressive symptoms and their adaptation to their lives as a result of their improved awareness of their own and others' mind, increased knowledge about ASD, and enhanced coping skills for emotion-regulation. Thus, secondary outcome measures will be the scores of the TAS-20, the CISS and the ASD questionnaire and the percentage of correct response on the MPMR at 12 weeks follow-up and the scores of the State-trait Anxiety Inventory (STAI) [29], the LSAS [30], the SPAI [31], the Center for Epidemiological Studies Depression Scale (CES-D) [32], the Global Assessment of Functioning, Japanese version (GAF) [18] and the World Health Organization Quality of Life 26-item version, Japanese version (WHO-QOL 26) [33] at post-intervention and 12 weeks follow-up. These measures are described in greater detail below.

The STAI is a self-report questionnaire that includes separate measures for state and trait of anxiety. The

STAI consists of 20 items each for state and trait of anxiety. Each item for state anxiety is rated from 1 (not at all) to 4 (very much so) and each item for trait anxiety is rated from 1 (almost never) to 4 (almost always). The total score for each ranges from 20 to 80. The time required for this test is about 10 minutes.

The SPAI is a self-report questionnaire that assesses specific somatic symptoms, cognitions, and behaviors across a wide range of potentially fear-inducing situations to measure social anxiety and fear. The SPAI consists of 109 items and two domains: social phobia and agoraphobia. Each item is rated from 0 (never) to 6 (always). The social phobia score ranges from 0 to 192 and the agoraphobia score ranges from 0 to 78. The time required for this test is about 25 minutes.

The LSAS is a questionnaire designed to assess the range of social interactions and performance situations that individuals with social phobia may fear and/or avoid. This measure was designed as a self-report questionnaire, but we use it here in the form of an interview. The LSAS comprises 24 social situations that are each rated for level of fear (0 = none to 3 = severe) and avoidance (0 = none to 3 = usually). The total score ranges from 0 to 144. The time required for the interview is about 10 minutes.

The CES-D is a self-report screening tool for depression and consists of 20 items. Each item is rated from 1 (absent) to 4 (five or more times a week), and the total score ranges from 0 to 60. The time required for this test is about 5 minutes.

The GAF is used by clinicians to make a global assessment of an individual's adaptive level of functioning on a scale from 0 (poor) to 100 (good). The time required for this interview is about 30 minutes.

The WHO-QOL 26 is used to measure an individual's subjective sense of wellbeing and quality of life, rather than determining the possible presence of an illness. The WHO-QOL 26 consists of 26 items and four domains: physical health, psychological health, social relationships, and environment. Each item is rated from 1 (poor) to 5 (good) and presented as an average score. The time required for this test is about 5 minutes.

It takes about 1 hour for the participant to fill out all of the questionnaires; therefore, they will be sent via mail to their home 7 to 10 days before the assessment date with careful consideration of the participants' burden. During the pre-, post-, and follow-up assessments, the GAF and LSAS interviews will take about 30 minutes. The theory of mind tasks, MPMR (done on a PC) will take about 15 minutes.

Details of the intervention program

The CBT group will receive group therapy over an 8 week period (1 session/week) with each session lasting approximately 100 minutes. Each session will include a short