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 U.S. norms (the SRS manual, p.28)[11] and the obtained Japanese scores using *t*-tests. Factor analysis was performed using principal components analysis (PCA) on children in the ASD, non-ASD, and TD groups, and the most parsimonious model was subsequently examined by confirmatory factor analysis in the normative sample. To address discriminant validity, comparisons of the SRS scores across diagnostic groups were conducted 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 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, with AMOS 17.0J for Windows used for the confirmatory factor analysis.

RESULTS

Population distribution—SRS score distribution among 6- to 15-year-old children in the Japanese general population is shown in Figure 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 × sex) was conducted on the total raw scores. The interaction was significant ($F_{(8,180,224)} = 2.00, p < .05, \eta^2 = .00$), and the main effects of grade ($F_{(8,180,224)} = 20.03, p < .001, \eta^2 = .01$) and sex ($F_{(8,180,224)} = 157.37$, $p < .001, \eta^2 = .01$) 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 ($t = 44.24, p < .001, d = .25$). 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 U.S. parent and teacher rating data (the SRS manual, p.28)[11] derived from five different studies. Japanese children scored similarly to their U.S. counterparts, except those in grades 4 and 9; here Japanese children had significantly lower mean SRS scores than their U.S. 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 U.S. 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[21,25] was subjected to confirmatory factor analysis 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 5 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.

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 < .001, d = .65, girls t =4.68 , p < .001, d = .83) and TD (boys t =11.73 , p < .001, d=2.29, girls t =11.80 , p < .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.[24] As shown in Figure 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 to males.

SRS score did not correlate with IQ (ICC = −.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 = .66, p < .001; Figure 3), as well as scores for the social interaction domain (ICC = .68, p < .001), communication domain (ICC = .58, p < .001), and restricted and repetitive behavior domain (ICC = .50, p < .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).

ROC 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 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 (eg. 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 (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 demonstrated overlap in causal influence on autistic symptomatology at each of the first, second, and fifth percentiles of severity in the population.[33]

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 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%, respectively 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 traits 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 U.S. dataset[11] (d=0.37) but similar to the German normative sample[24] (d=0.16). Accentuation of the gender difference in the U.S. dataset 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 U.S. 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 U.S. 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 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 psychopathology when they co-occur 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.[1,19,20,37] 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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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 U.S. and European samples.
- Autistic traits measured quantitatively by parents differ slightly by culture, suggesting the need to interpret autism spectrum disorders (ASD) severity ratings with the use of culturally calibrated norms.
- #x02022; 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 versus 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.

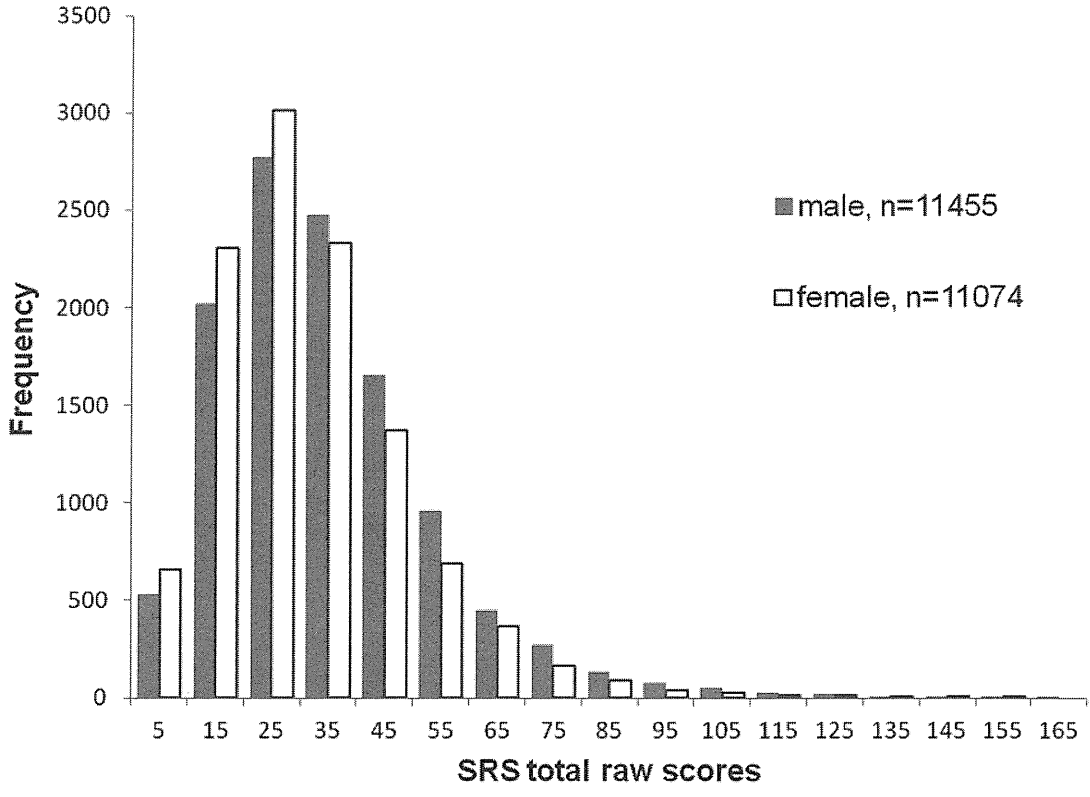

Figure 1.
Distribution of Social Responsiveness Scale (SRS) total raw scores rated by caregivers in the general sample of 6- to 15-year-old children

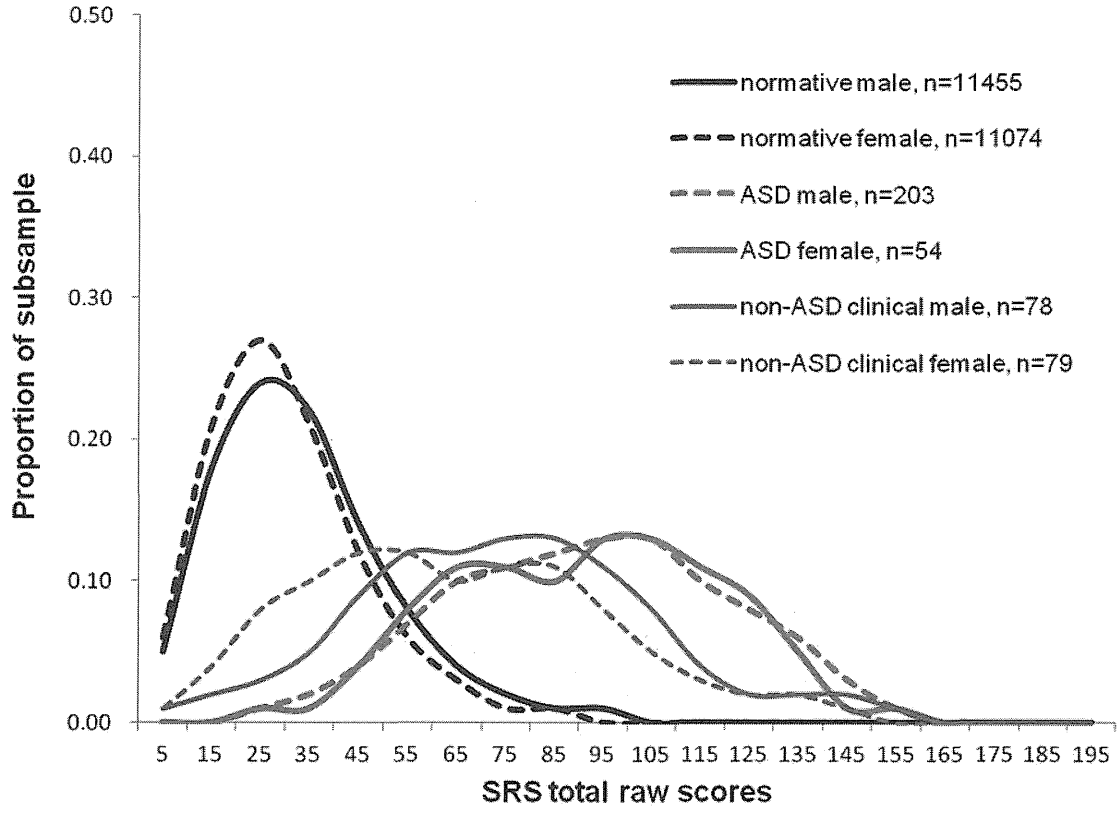

Figure 2.
Distribution of SRS total raw scores in child psychiatric patients with and without autistic spectrum disorders (ASD)

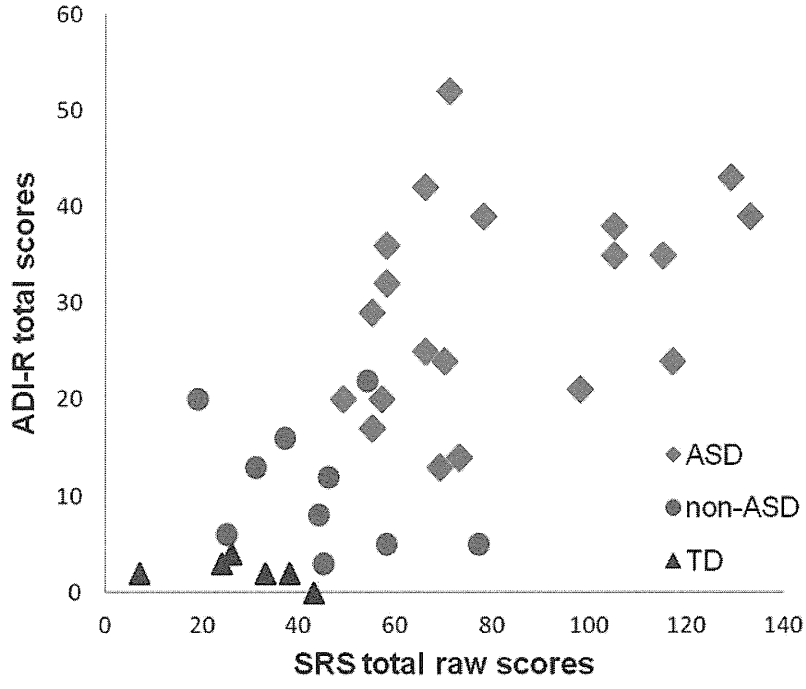

Figure 3.
SRS total raw scores as a function of Autism Diagnostic Interview-Revised (ADI-R) total scores for children with ASD, non-ASD, and typical development (TD)

Table 1

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

	N	Mean (SD)	N	Mean (SD)	*t*	*p*	*d*
Sex							
Grade	**Males**		**Females**				
1	1,655	37.3 (18.2)	1,473	33.0 (16.7)	44.3	0.000	0.25
2	1,521	36.2 (18.2)	1,394	32.1 (16.3)	37.8	0.000	0.24
3	1,384	35.4 (19.2)	1,432	31.2 (16.4)	39.0	0.000	0.24
4	1,375	33.7 (18.4)	1,386	30.2 (16.3)	26.2	0.000	0.20
5	1,449	33.0 (18.5)	1,287	31.0 (17.5)	8.6	0.003	0.11
6	1,203	31.9 (19.6)	1,229	29.9 (17.8)	6.9	0.009	0.11
7	1,072	32.3 (19.1)	1,070	30.3 (17.8)	6.7	0.010	0.11
8	1,007	32.7 (20.2)	1,049	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)					

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

Table 2

Comparison of Social Responsiveness Scale total raw score between the U.S. and Japan.

	N	Mean (SD)	N	Mean (SD)	*t*	*p*	*d*
Country							
Grade	**Japan**		**U.S.**				
1	3,102	35.3 (17.6)	71	29.6 (25.6)	1.87	0.06	0.318
2	2,891	34.2 (17.4)	92	34.9 (26.9)	0.25	0.80	0.041
3	2,786	33.2 (18.0)	109	35.7 (26.8)	0.97	0.33	0.136
4	2,739	31.9 (17.5)	227	35.3 (24.9)	2.02	0.04	0.188
5	2,703	32.0 (18.0)	214	34.5 (25.3)	1.42	0.16	0.134
6	2,408	30.8 (18.7)	211	31.7 (21.5)	0.59	0.56	0.049
7	2,123	31.3 (18.4)	161	31.1 (20.6)	0.12	0.90	0.008
8	2,040	31.1 (19.1)	137	31.9 (23.7)	0.39	0.70	0.040
9	1,532	30.2 (19.7)	124	38.9 (29.2)	3.26	0.00	0.422
Total	22,342	32.5(18.2)	1,626[a]	33.6(24.7)	1.76	0.08	0.051

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

[a]U.S. data were cited from the SRS manual (p.28)[11]).

Table 3

Principal components analysis of Social Responsiveness Scale data.

	ASD, non-ASD, and TD groups (n=475)		
Component	**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

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

ASD=autism spectrum disorders, TD=typical development

Table 4

SRS total raw score means of the ASD, non-ASD, and TD groups.

	ASD	nonASD	TD	ASD subcategory			
				Autism	Asperger's disorder	PDD-NOS	unspecified
N (Male: Female)	257 (203 : 54)	157 (78 : 79)	61 (30 : 31)	96 (77 : 19)	65 (48 : 17)	68 (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
Intellecual level (N)							
Normal	181	118	57	57	64	59	1
Borderline	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	2	0	0	10
MR(unknown level)	33	7	0	22	0	2	9
SRS Mean (SD) Range							
Males	87.6 (27.4) 15–158[a]	69.7 (27.9) 13–141 [a]	27.4 (16.6) 6–72 [a]	89.5 (24.0) 48–139[d]	82.4 (26.8) 15–132	78.4 (26.5) 24–144 [d]	
Females	86.1 (27.9) 21–153[b]	62.1 (29.9) 12–134 [b]	21.4 (16.2) 2–65 [b]	91.4 (27.2) 21–133	91.0 (31.4) 38–153	74.7 (25.3) 40–114	
Total	87.3 (27.4) 15–158[c]	65.9 (29.1) 12–141[c]	24.3 (16.5) 2–72 [c]	89.8 (24.5) 21–139[e]	84.6 (28.1) 15–153	77.7 (26.1) 24–144[e]	

Note: SRS=Social Responsiveness Scale, ASD=autism spectrum disorders, TD=typical development; PDD-NOS=Pervasive Developmental Disorder Not Otherwise Specified; MR=mental retardation

[a] ASD>non-ASD, TD (t=4.87, p<.001, d=.65;t=11.73, p<.001, d=2.29, respectively), non-ASD>TD (t=7.79, p<.001, d=1.67);

[b] ASD>non-ASD, TD (t=4.68, p<.001, d=.83; t=11.80, p<.001, d=2.66, respectively), non-ASD>TD (t=7.17, p<.001, d=1.52);

[c] ASD>non-ASD, TD (t=7.53, p<.001, d=0.76; t=17.19, p<.001, d=2.45, respectively), non-ASD>TD (t=10.51, p<.001, d=1.59);

[d] Autism>PDD-NOS (t=2.48, p<.05, d=.44);

[e] Autism>PDD-NOS (t=3.05, p<.05, d= .48)

Table 5

Proportion of children with ASD corresponding to the 99th, 97.5th, 95th, and 90th percentile values among the ASD group of the Japanese clinical sample

Normative sample (n=22,529)			ASD group (n=257)			
	Raw score cutoff		N, %			
Percentile value	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%

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Prepulse Inhibition of Startle Response: Recent Advances in Human Studies of Psychiatric Disease

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Prepulse inhibition (PPI) is considered to be one of the most promising neurophysiological indexes for translational research in psychiatry. Impairment of PPI has been reported in several psychiatric diseases, particularly schizophrenia, where PPI is considered a candidate intermediate phenotype (endophenotype) of the disease. Recent findings from a variety of research areas have provided important evidence regarding PPI impairment. Human brain imaging studies have demonstrated the involvement of the striatum, hippocampus, thalamus and frontal and parietal cortical regions in PPI. In addition, several genetic polymorphisms, including variations in the genes coding for Catechol O-methyltransferase, Neuregulin 1, nuclear factor kappa-B subunit 3 and serotonin-2A receptor were related to PPI; and these findings support PPI as a polygenetic trait that involves several neurotransmitter pathways. Early psychosis studies suggest that PPI disruption is present before the onset of psychosis. Also, discrepancy of PPI impairment between children and adults can be found in other psychiatric diseases, such as autistic spectrum disorders and posttraumatic stress disorder, and comprehensive investigation of startle response might contribute to understand the impairment of the neural circuitry in psychiatric diseases. Finally, recent studies with both Asian and Caucasian subjects indicate that patients with schizophrenia exhibit impaired PPI, and impaired sensorimotor gating might be a global common psychophysiological feature of schizophrenia. In conclusion, studies of PPI have successfully contributed to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating and will certainly be most valuable in devising future approaches that aim to investigate the complex pathogenesis of psychiatric diseases.

KEY WORDS: Endophenotypes; Mental disorders; Psychophysiology; Schizophrenia; Startle reaction.

INTRODUCTION

To understand the complex pathogenesis of genetic and environmental interaction underlying psychiatric disease has been set as a critical goal, as hopes on translational research that combines both basic and clinical researchers have soared.

Prepulse inhibition (PPI) is considered to be one of the most promising neurophysiological indexes for translational research in psychiatry. Impairment of PPI is reported in several psychiatric diseases,[1] of which schizophrenia is the most prominent. Other diseases include anxiety disorders, such as obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD), and developmental disorders, such as autistic spectrum disorders (ASD).

Although PPI is a well established index,[2-5] there is still a vast number of research areas where the potential beneficial use of PPI has not been investigated. In this review, we briefly overview the well described applications of PPI and then discuss some recent advances in human PPI studies, including research on brain imaging, genetic analyses and comparison of PPI in different populations, at different ages.

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A BRIEF OVERVIEW OF PPI IN HUMAN SUBJECTS

PPI is usually defined as a reduction of the startle reflex due to weak sensory prestimulation.[6] PPI is considered to be the most common psychophysiological index of sensorimotor gating, which is an autonomic inhibition system that regulates sensory input by filtering out irrelevant or distracting stimuli. This prevents overflow of sensory information and allows for the selective and efficient processing of relevant information.[6-8] PPI is elicited by any kind of stimuli, including visual, acoustic, tactile or olfactory stimuli. Acoustic stimuli are usually used for experiments, and the majority of human studies measure orbicularis oculi muscle electromyographic activity of blink reflex induced by acoustic startle stimuli.[9] As PPI can be assessed using simple nonlinguistic stimuli, PPI is widely investigated across races[10-12] and species (animals,[3-5,13-15] such as rats or mouse), using similar experimental paradigms.

Although PPI is considered to be a stable index of individual sensorimotor gating,[16] several factors can affect its measurement. Some of the most relevant include gender, smoking and medication, in particular antipsychotic medication. Gender-related differences in PPI have been reported in normal subjects, with levels of PPI in women lower than in men.[17-24] In addition, women present fluctuations of PPI across the menstrual cycle,[25] with the lowest levels manifested in the mid-luteal phase.[18] PPI can also be enhanced by smoking[26-29]; however, this effect appears to be of short term duration (less than 10 minutes).[21] Some studies also reported the effects of substances such as caffeine,[30,31] cannabis,[32,33] and amphetamines,[34,35] on PPI. Finally, PPI is considered to be affected by the medication status and to involve several neurotransmitter pathways,[2,36-39] including the dopaminergic, glutamatergic, serotonergic and cholinergic pathways. This will be a matter of further discussion in the following sections.

PPI IN SCHIZOPHRENIA

Schizophrenia is one of the most prominent psychiatric diseases presenting deficits in PPI. Impaired sensorimotor gating has been considered to be a common psychophysiological feature of schizophrenia that may, theoretically, lead to severe dysfunctions in perception, attention and thinking.[40,41] Since Braff *et al.*[6] reported PPI reduction in schizophrenic patients, that reductions of PPI have been consistently demonstrated in schizophrenia.[2,38,42]

Recently, PPI has been considered a promising candidate intermediate phenotype (endophenotype) of schizophrenia.[43-46] PPI is not only reduced in schizophrenia patients but also in unaffected relatives,[47,48] and it has showed substantial heritability of 32-50%.[45,49,50] Deficient PPI has also been observed in patients with schizotypal personality disorder[47,51,52] and, to a lesser extent, in normal participants scoring high on psychometric measures of psychosis proneness.[53-55] Although the profile of startle measures is thought to differ across races,[10-12] patients with schizophrenia consistently had reduced PPI compared to normal controls in recent studies with Asian subjects.[56-58]

Numerous studies have provided evidence that PPI deficits in patients with schizophrenia are improved by antipsychotics,[24,37,38,40,42,59-67] in particular atypical antipsychotics, which appear to have a close association with PPI improvement in schizophrenia.[24,42,59-61,63,64,66,68-70] Although PPI has been reported in association with positive symptoms[65,71] and negative symptoms,[71,72] thought disorders[73] and social perception[74] of schizophrenia, most studies do not support a link between PPI and psychiatric symptoms.[24,63,70,75] However, this might be explained by the medication status of the patients, which is known to affect the relationship of psychiatric symptoms with PPI in schizophrenia.[76] While antipsychotic-naive schizophrenia patients[65,68,77-80] present PPI deficits, antipsychotic medication eliminates the impairment of PPI.[78,79] Vollenweider *et al.*[81] has suggested that clozapine enhances PPI in healthy humans with low but not with high PPI levels. On the other hand, haloperidol failed to increase PPI in subjects exhibiting low levels of PPI, despite the fact that PPI was attenuated in those subjects with high sensorimotor gating levels.[82] Therefore, the effect of antipsychotics on PPI might differ depending on the medication or the severity of the PPI deficits.[81,82] Longitudinal studies evaluating PPI before and after medication will help to elucidate the effect of antipsychotics on PPI in schizophrenia.

BRAIN AREAS INVOLVED IN PPI

In order to comprehend the physiological nature of PPI it is necessary to investigate the areas of the brain that are required during PPI. In experimental animals,[37,40,83] the cortico-striato-pallido-thalamic circuitry is thought to be responsible for modulation of PPI. A recent study[84] has shown that some forebrain areas are involved in top-down modulation of PPI. Recently, human brain imaging stud-

ies of PPI using several approaches, such as positron emission tomography and anatomical/functional magnetic resonance imaging (MRI), provided important evidence to understand the neurophysiological mechanisms of PPI.

The Kumari *et al.*[85] research group has published numerous important studies that addressed the biological nature of PPI. In an MRI volumetric voxel-based morphometry study, healthy subjects showed significant positive correlations between PPI and grey matter volume in the hippocampus extending to parahippocampal gyrus, basal ganglia, including parts of putamen, globus pallidus, and nucleus accumbens, superior temporal gyrus, thalamus, and inferior frontal gyrus. Patients with schizophrenia[86] showed significantly positive correlations between PPI and grey matter volume in the dorsolateral prefrontal, middle frontal and the orbital/medial prefrontal cortices. Functional MRI (fMRI) studies[87,88] showed that the PPI of healthy subjects was associated with increased activation in the striatum extending to hippocampus and thalamus, inferior frontal and inferior parietal regions, and that all activated regions had significantly greater response in healthy subjects than schizophrenic patients.[88] Patients treated with risperidone or olanzapine, but not with typical antipsychotics, showed significant activation in the PPI-relevant regions.[87]

Other research groups have found similar results. In an fMRI study of Campbell *et al.*,[89] PPI was found associated with activation in pons, thalamus, caudate nuclei, left angular gyrus and bilaterally in anterior cingulate. Also by fMRI, Hazlett *et al.*[90] showed that, using attend/ignore PPI paradigm, lower left caudate activation during the attended PPI condition was associated with more deficient sensorimotor gating among schizotypal personality disorder, schizophrenia, and healthy controls. In a PET[91] study, normal controls showed a positive association between PPI and metabolic activity rates of glucose in prefrontal (Brodmann's areas 8, 9, and 10 bilaterally) and lower in visual cortex, while patients only showed this association for area 10 in the left hemisphere.

These findings demonstrate the involvement of the striatum, hippocampus, thalamus, and frontal and parietal cortical regions in PPI. Dysfunctions in any of these regions may underlie observations of reduced PPI in psychiatric diseases, including schizophrenia, which might be improved by atypical antipsychotic medication.

GENETIC BASIS OF PPI

The use of PPI as an endophenotype in schizophrenia has been recently becoming consensual.[44,46,92] As PPI can be easily measured, it has the advantage to collect large sample sizes necessary for genetic approaches that conduct multi-site studies.[12] Several research groups have been investigating the relationship between PPI and the genome.

Roussos *et al.* and Giakoumaki *et al.*[93-96] have reported associations of PPI with several genotypes in healthy males. Examination of the Catechol O-methyltransferase (*COMT*) Val158Met polymorphism,[93] the main catabolic pathway of released dopamine (DA) in the prefrontal cortex (PFC), showed that Val (low PFC DA) /Val individuals had the lowest PPI, Met (high PFC DA)/Met the highest, and Val/Met were intermediate. In addition, the non-stimulant *COMT* inhibitor tolcapone increased PPI significantly in the Val/Val group and tended to have the opposite effect in the Met/Met group.[94] In a study examining the influence of the Dopamine D3 receptor Ser9Gly polymorphism on human PPI,[95] Gly/Gly individuals had the lowest PPI and Ser/Ser individuals had the highest PPI, while Ser/Gly individuals were intermediate. Investigation of the relationship between PPI and haplotypes comprising three Proline dehydrogenase (oxidase 1) single nucleotide polymorphisms (SNPs; 1945T/C, 1766A/G, 1852G/A) located in the 3' region of the gene,[96] CGA carriers, which are preferentially transmitted in schizophrenia patients,[97,98] exhibited attenuated PPI compared with the noncarriers. Furthermore, Roussos *et al.* examined the relevance for PPI of SNPs in promising schizophrenia risk genes, such as the D-amino acid oxidase (*DAO*) gene (rs4623951, rs2111902, rs3918346, rs3741775, and rs3825251)[99] and the Neuregulin 1 (*NRG1*) gene (rs6994992, SNP8NRG221132, SNP8NRG241930, rs3924999, rs2439272 and rs10503929),[100] and reported that reduced PPI was associated to the rs4623951_T-rs3741775_G and rs4623951_T-rs2111902_T diplotypes of *DAO* gene,[99] and to the SNP8NRG241930 G allele and particularly the rs6994992 T allele and rs2439272 C allele *NRG1* gene.[100]

The laboratory of Quednow *et al.*[101-103] has reported associations of PPI with several genotypes in both healthy subjects and patients with schizophrenia. An association of PPI with the serotonin-2A receptor (*5-HT$_{2A}$R*) A1438G/T102C (rs6311/rs6313), *COMT* Val158Met (rs4680) and *NRG1* Arg38Gln (rs3924999) were investigated in healthy Caucasian subjects,[101] and increased PPI levels were found in homozygous for the *5-HT$_{2A}$R* T102C-T/A-1438 G-A allele. Increased PPI levels were also found in male subjects with the *COMT* Met158Met-

genotype, but no significant association of PPI with the *NRG1* Arg38Gln genotype was detected. Investigation of the impact of three *5-HT$_{2A}$R* polymorphisms (A-1438G, T102C, H452Y) on PPI in Caucasian schizophrenia patients[102] showed that patients carrying the T102C TT and the A-1438G AA allele present significantly higher PPI levels compared with all other variants. In contrast, the H452Y polymorphism did not affect PPI. Quednow *et al.*[103] also investigated the impact of the *COMT* Val158Met polymorphisms on PPI in Caucasian schizophrenic inpatients, and reported that patients carrying the Met/Met allele showed elevated PPI levels compared to other two genotypes. PPI was also influenced by two common nicotinic acetylcholine receptor (nAChR) α3 subunit (*CHRNA3*) polymorphism (rs1051730/rs1317286) in healthy subjects and in patients with schizophrenia.[104] Recently,[105] the impact of the transcription factor 4 (TCF4) gene (rs9960767), a susceptibility gene for schizophrenia, on PPI was investigated in healthy subjects and in a schizophrenia spectrum group (including schizophrenia patients and individuals at high risk for schizophrenia), and in both samples PPI was strongly decreased in carriers of the schizophrenia risk allele C of the TCF4 gene.

Hong *et al.*[106] examined the effects of the *NRG1* Arg38Gln polymorphism on PPI in patients with schizophrenia and in normal controls. They reported that PPI was lowest in the subjects who were homozygous for the minor allele A/A carriers, intermediate in A/G carriers and highest in homozygous major alleles G/G carriers in both patient and control groups. Greenbaum *et al.*[107] reported an association of the reelin SNP rs7341475 with PPI. In addition, Hokyo *et al.*[108] reported that, in both healthy subjects and patients with schizophrenia, human N-methyl-D-aspartate (NMDA) receptor 2B subunit gene (*GRIN2B*) polymorphism rs1019385 (T200G) did not show any significant influence on PPI, although it was significantly related to habituation of startle response. Finally, Hashimoto *et al.*[109] reported that PPI deficits in schizophrenia were associated with PPI schizophrenia risk genotypes of three SNPs (rs11820062, rs2306365, rs7119750) in the v-rel avian reticuloendotheliosis viral oncogene homolog A gene, which encodes the major component of the Nuclear factor kappa B (NF-κB) complex.

All together, these data strongly support PPI as a polygenetic trait that involves several neurotransmitter pathways and the use of PPI as a valid schizophrenia endophenotype. However, as noted previously, PPI can be affected by several factors, such as gender, smoking status and antipsychotic medication, and future studies with large sample sizes that consider these effects are deemed required. Investigation of mechanism how these factors effect on PPI across genotypes will contribute to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating and will certainly be most valuable in devising future approaches that aim to investigate the complex pathogenesis of psychiatric diseases.

EARLY PSYCHOSIS AND PPI

Research on early psychosis (ER) has been growing and PPI might also play an important role in this field.

In a 2-year follow-up study,[110] comparing ultra-high risk (UHR) adolescents with matched control group, UHR individuals showed reduced PPI at both baseline and 2 years compared with controls. Clinical improvement in UHR individuals was associated with an increase in PPI parameters. In another study,[111] PPI of acoustic startle response was assessed in subjects with prodromal symptoms of schizophrenia, first-episode schizophrenia patients and healthy control subjects. Prodromal subjects and unmedicated patients with first-episode schizophrenia showed significant PPI deficits, whereas schizophrenia patients treated with risperidone had almost normal PPI. These studies, together with the evidence that antipsychotic-naive schizophrenia patients[65,68,77-80] present PPI impairment, suggest that PPI disruption might be already present before the onset of psychosis and that PPI may represent a vulnerability marker for psychosis.

Intriguing results were found in a study[112] investigating PPI in EP, at risk (AR) for psychosis and comparison subjects at baseline and 6 months later. PPI was stable with repeated assessment and EP subjects had reduced PPI. The unexpected findings regard the fact that medication-naive EP subjects, as well as AR subjects who later developed psychosis, had greater PPI compared to EP subjects with antipsychotic medication, and to AR subjects who did not develop psychosis, respectively, introducing the possibility of early compensatory changes that diverge from findings in chronic patients. Therefore, longitudinal studies following up the pathological change of startle modulation in a long period prior to the onset of the disease are required to determine the use of PPI for early detection of psychosis.