Participants in the nonclinical control group were recruited from the local communities by individual examiners at locations such as schools, daycare centers, universities, offices, parents' circles, and neighborhood organizations. Individuals were excluded from the nonclinical control group if they had a clinical diagnosis of any psychiatric disease. IQs were not recorded for the nonclinical control group because they did not have histories of any psychiatric problems or special needs education and were considered to have normal intellectual ability.

Furthermore, separate from the main sample, data from 56 participants (mean age = 9.2 years; SD = 5.8; range = 3–26 years) diagnosed as having PDD by experienced psychiatrists were analysed to evaluate the inter-rater reliability of PARS.

The protocol of this study was approved by the institutional review board of Hamamatsu University School of Medicine.

2.3. Procedure

Psychiatrists, clinical psychologists, and graduate students involved in the service for developmental disorders administered the PARS interview by referring to the manual. They had undergone a brief training, which had the following agenda: (a) a lecture on psychiatric features of individuals with PDD; (b) instructions on the rating criterion of each item of PARS; and (c) open completion, scoring, and discussion of the interview. They conducted the PARS interview with the informants (many of whom were parents) after obtaining the appropriate informed consent. The interviewers were not completely blind to the probands' diagnosis because some of them recruited participants themselves. For some participants, an additional ADI-R interview was implemented by Japanese interviewers who had undergone a three-day long ADI-R training workshop in the United States to learn the implementation and scoring methods of ADI-R (Lord et al., 1994). They created a Japanese translation of the ADI-R and received permission from the original author and the publisher to use it through a validation process based on Japanese sample (Tsuchiya et al., submitted for publication). The ADI-R generates algorithm scores for each of the three subdomains; (a) qualitative impairments in reciprocal social behavior; (b) delays in language development; and (c) restricted range of interest and/or stereotypic behaviors. The item composition of the subdomain of delays in language development differs depending on whether or not a subject can use language. We implemented ADI-R only for subjects who can use language.

For the sample used for evaluation of inter-rater reliability, PARS was administered independently to each informant by two interviewers (one experienced specialist and one less experienced trainee).

2.4. Statistical analyses

A comprehensive examination of the reliability and validity of PARS was conducted in five steps. First, to consider the inter-rater reliability of PARS, the correlation coefficient between the scores recorded by the two interviewers of the same subject was calculated. Second, to examine the factor structure of PARS, exploratory factor analysis (mean-adjusted weight least-square estimation with promax rotation) was performed based on the PDD group data, and four subscales were extracted. As the score for each item was considered as an ordered categorical variable of three values, factor analysis was carried out using the polychoric correlation coefficient (see Holgado-Tello, Chacon-Moscoso, Barbero-Garcia, & Vila-Abad, 2010). Third, the α coefficient was calculated based on data of the PDD group to examine the internal consistency of the overall scale and four subscales. Fourth, to examine convergent validity, correlation of PARS scores with the ADI-R algorithm scores was considered using Pearson's coefficient.

Fifth, to consider how well PARS distinguishes between PDD and non-PDD, *t*-tests and receiver operating characteristic (ROC) analysis (Swets, 1988) were performed. ROC analysis plots the curve (ROC curve) of the true positive rate (sensitivity) vs. the false positive rate (one minus specificity) as the discrimination cutoff value is varied. The larger the area under the ROC curve (AUC), the higher the discriminative power of the scale. In general, sensitivity and specificity are in a trade-off relationship, and the two cannot be simultaneously maximized. In the present study, the cutoff value was set at the point where the sum of sensitivity and specificity was the largest, and sensitivity and specificity for that point were reported. Further analysis including the presence of mental retardation (MR) as a variable was conducted to consider whether the discriminative power of PARS is influenced by IQ level.

Before initiating the abovementioned analyses, we examined the difference in the scale scores for the 3 age groups because previous studies (Adachi et al., 2006; Kamio et al., 2006; Tsujii et al., 2006) have examined the scale properties of the PARS separately for each age group. One-way ANOVA showed that the total PARS score did not significantly differ for the 3 age groups, both in the PDD group, $F(2, 280) = .41$, $p = .66$, and in the control group, $F(2, 315) = 2.49$, $p = .08$. Therefore, we decided to perform the analyses without any distinction between the age groups.

Significance levels of statistical tests were set at 5% and 1%. Mplus (Muthén & Muthén, 1998–2007) was used for factor analysis, and SPSS 15.0J (SPSS Inc., 2006) was used for other analyses.

3. Results

3.1. Inter-rater reliability

Spearman's rank correlation coefficients between the scores of two interviewers were significant for all items ($p < .05$ in item 27; $p < .01$ in remaining items), with an average value of .68 (SD = .11). For the total score, the Pearson's correlation coefficient between the scores of the interviewers was $r = .78$ ($p < .01$).

Table 2
Corrected item-total correlations and factor loadings.

No.	Item	I-T corr.[a]	Factor loading			
			F1 SC[b]	F2 SD[c]	F3 SB[d]	F4 RI[e]
5	Does not communicate interest by pointing	.70	**.83**	.17	.01	−.20
6	Verbal development is delayed	.71	**.82**	−.29	.00	.09
7	Conversation does not continue	.79	**.81**	−.22	.03	.29
4	Does not bring items to show	.67	**.79**	.16	.08	−.23
1	Does not make eye contact	.74	**.69**	−.01	.06	.04
2	Is not interested in other children	.74	**.62**	.23	−.02	−.05
9	Does not play with other children	.79	**.57**	.08	.15	.06
3	Does not look back when name is called	.70	**.53**	.02	.20	.06
28	Becomes unstable bringing back to unpleasant memories	.53	−.20	**.82**	−.06	−.01
26	Becomes confused when everyday situations or routines changes	.69	.06	**.67**	−.12	.06
33	Suddenly cries or becomes upset	.60	.12	**.62**	.02	.05
32	Is very scared over nothing	.54	−.10	**.60**	−.06	.18
34	Show self-injurious action like banging head on wall or chewing hands	.46	.01	**.41**	.26	−.15
27	Cannot maintain personal independence due to disrupted lifestyle	.41	−.17	**.40**	.25	−.19
30	Disturbed by particular sounds	.63	−.03	**.37**	.19	.21
24	Does not like to be touched	.58	.14	**.37**	.20	.10
31	Is either insensitive or oversensitive to pain, heat, etc.	.62	−.15	**.36**	.28	.03
20	Does not like to be held	.56	.18	**.25**	.16	.17
22	Turns pages or crumples paper repeatedly in the same way	.54	−.03	−.14	**.67**	.23
19	Eats or swallows nonfood items	.37	.00	−.05	**.66**	−.22
14	Likes watching things that revolve	.59	.03	−.05	**.66**	.13
18	Is hyperactive and may go anywhere if left unattended	.62	.05	−.20	**.65**	−.02
17	Walks on tiptoes	.47	−.01	−.01	**.60**	−.18
23	Moves entire or part of the body repeatedly in the same pattern	.56	.03	.07	**.54**	.06
12	Becomes immersed in sensory play	.61	.15	−.05	**.51**	.06
15	Looks at things from the corner of eye or from extremely close	.62	.15	−.03	**.48**	.23
11	Repeats the words of commercials, etc.	.61	−.08	−.06	.00	**.81**
10	Parrot-like repetition stands out	.68	.37	−.10	−.08	**.68**
13	Loves road signs, logos, numbers, and letters	.59	−.13	.09	.06	**.60**
8	Speaks only one way to say what he/she wants	.70	.09	.04	−.06	**.51**
21	Repeatedly watches specific scenes of videos	.62	−.11	.15	.14	**.49**
25	Persistently asks the same question	.48	−.28	.19	.00	**.38**
16	Becomes immersed lining up toys and bottles	.61	.05	.21	.03	**.34**
29	Extremely unbalanced diet, eats very few food items	.57	.03	.18	.11	**.24**

	Interfactor correlations			
	F1	F2	F3	F4
F2	.25			
F3	.45	.50	–	
F4	.27	.42	.33	–

Bold loadings indicate grouping in sub-scales.
[a] Corrected item-total correlation.
[b] Social Communication.
[c] Sensitivity/Difficulty.
[d] Stereotyped Behavior.
[e] Restricted Interests.

3.2. Factor structure and internal consistency

Table 2 shows the corrected item-total correlation for each item and the results of factor analysis. Based on a scree plot (9.25, 3.76, 2.36, 2.02, 1.68, 1.62, ...) that showed a leveling-off of eigenvalues after the fourth factor (cf. Cattell, 1966) and perceived interpretability, a four-factor solution was employed. The four factors explained 42.27% of the variability of the total score, and each factor was named in decreasing order according to the factor loading of the items grouped in the factor, starting with Social Communication, Sensitivity/Difficulty, Stereotyped Behavior, and Restricted Interests. The α coefficient based on data of the PDD group was .84 for the communication scale (8 items), .74 for the sensitivity/difficulty scale (10 items), .72 for the stereotyped behavior scale (8 items), and .70 for the Restricted Interests scale (8 items). The α coefficient for all scales was .86. All of the individual item-to-total score correlations were positive and mainly substantial, in the range of .37–.79 (29 of the 34 exceeding .50). The mean values for each subscale and the total score for each group are shown in Table 3.

3.3. Correlation with the ADI-R

The correlation of PARS subscores and total score with ADI-R domain scores and total score is shown in Table 4. The score of Qualitative Abnormalities in Reciprocal Social Interaction in ADI-R showed moderate correlation with the score of Social

Table 3
Means and standard deviations of PARS total score and subscores.

	Social Communication		Sensitivity/ Difficulty		Stereotyped Behavior		Restricted Interest		Total sore	
	M[a]	SD[b]	*M*	SD	*M*	SD	*M*	SD	*M*	SD
PDD[c] group	10.03	4.62	7.36	4.61	6.12	4.02	7.96	4.09	31.46	12.52
Without MR[d] (IQ ≥ 70)	8.83	4.37	7.04	4.99	5.46	3.68	8.11	4.23	29.45	13.00
With MR (IQ < 70)	12.66	3.18	7.83	4.39	8.21	4.12	8.45	4.17	37.14	11.55
Nonclinical control group	0.38	1.19	0.43	1.05	0.54	1.07	0.88	1.50	2.23	3.64

[a] Mean.
[b] Standard deviation.
[c] Pervasive development disorders.
[d] Mental retardation.

Table 4
Correlations between the ADI-R and PARS.

PARS	ADI-R			
	Social Interaction[a]	Communication[b]	Stereotyped Behavior[c]	Total score
Social Communication	.48**	.43**	.07	.48**
Sensitivity/Difficulty	.17	.03	.37**	.20
Stereotyped Behavior	.03	.27*	.42**	.25*
Restricted Interest	.07	.10	.41**	.19
Total score	.27**	.31**	.46**	.41**

[a] Qualitative abnormalities in reciprocal social interaction.
[b] Qualitative abnormalities in communication.
[c] Restricted, repetitive, and stereotyped patterns of behavior.
* $p < .05$.
** $p < .01$.

Communication in PARS. Furthermore, the score of Qualitative Abnormalities in Communication in the ADI-R showed moderate correlation with the score of Social Communication in PARS, and weak correlation with the score of Stereotyped Behavior and the total score in PARS. The score of Restricted, Repetitive, and Stereotyped Patterns of Behavior in the ADI-R showed weak correlation with the score of Sensitivity/Difficulty in PARS and moderate correlations with the score of Stereotyped Behavior and Restricted Interests and the total score in PARS. The total score of the ADI-R showed a moderate correlation with the score of Social Communication and the total score in PARS and a weak correlation with Stereotyped Behavior.

3.4. Discriminative validity

Table 5 and Fig. 1 shows the results of the *t*-test and ROC analysis between the PDD groups (whole group and without MR group) and the nonclinical control group. Three main points can be concluded from the table and figure. First, PARS shows high discriminative power even when the presence or absence of MR is controlled. Second, for either comparison, the total score has more discriminative power than the subscores. This is a general trend seen in other evaluation instruments such as

Table 5
Discriminative validity of the total and subscores of PARS.

	t[a]	AUC[b]	Cutoff point	Sensitivity	Specificity
PDD vs. nonclinical control					
Social Communication	33.9	.973	3	.929	.959
Sensitivity/Difficulty	24.6	.961	2	.921	.902
Stereotyped Behaviors	22.5	.928	2	.896	.851
Restricted Interests	27.2	.953	3	.875	.902
Total score	37.6	.991	9	.975	.956
PDD without MR vs. nonclinical control					
Social Communication	20.8	.964	3	.908	.959
Sensitivity/Difficulty	14.3	.949	2	.882	.902
Stereotyped Behaviors	14.4	.921	2	.882	.851
Restricted Interests	18.2	.952	3	.882	.902
Total score	22.5	.990	9	.975	.956

[a] All *t* values are significant at the 1% level.
[b] Area under the curve.

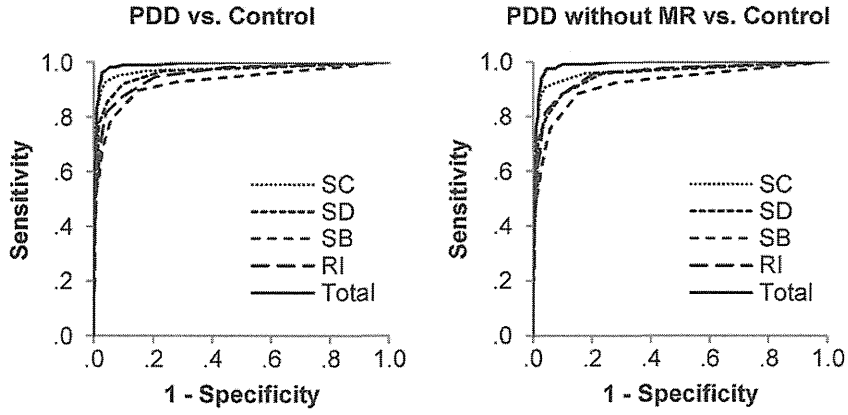

Fig. 1. Receiver operating characteristic curves for discrimination between normal control group and whole PDD (left) and PDD without MR group (right). SC, Social Communication; SD, Sensitivity/Difficulty; SB, Stereotyped Behaviors; RI, Restricted Interests.

the ADI-R (Lord et al., 1997) and ASQ (Berument et al., 1999). Third, the desired cutoff values are not affected by the presence or absence of MR.

4. Discussion

The objective of this study was to validate PARS, a scale developed for (1) the evaluation of PDD symptoms in a simpler manner than "gold standard" instruments, such as the ADI-R and ADOS, and (2) more objective evaluation than questionnaire scales, such as the ASSQ and ASQ. As long as the interviewer has a certain level of expertise pertaining to PDDs, PARS can be used after brief training and can be administered in an hour on an average by simplifying and structuring the interview procedure as much as possible and by using simple and clear terms in the manual. In this study, we administered PARS to individuals with PDD and nonclinical controls in order to examine its reliability and validity.

The rating scores recorded by two different interviewers of the same subject showed a sufficient correlation for individual items as well as for the overall score, demonstrating the inter-rater reliability of PARS. The developers of questionnaire scales have often criticized the form of the interview method, stating "the severity of each assessed behavior is rated by the interviewer 'second-hand' on the basis of the parent's answers" (Constantino et al., 2003). This criticism is based on the belief that the interview process produces random or systematic measurement error due to its "second-hand" nature. However, the PARS interview's high inter-rater reliability indicates that it produces little random error, probably because of each item's clearly defined rating criteria. We believe that a semi-structured interview conducted by specialists in treatment of developmental disorders will provide a more accurate measurement than a questionnaire scale based on the subjective judgments of people who lack specialized knowledge, as long as rating criteria are clearly defined and sufficient inter-rater reliability of the evaluation instrument is maintained.

Factor analysis extracted four subscales: Social Communication, Sensitivity/Difficulty, Stereotyped Behaviors, and Restricted Interests. The Social Communication scale corresponds to the "reciprocal social interaction skills" and "communication skills" criteria of the DSM-IV-TR (American Psychiatric Association, 2000), and the Stereotyped Behavior scale and the Restricted Interests scales correspond to the DSM-IV-TR's "presence of stereotyped behavior, interests, and activities." While there is no clear correspondence of the Sensitivity/Difficulty scale with the DSM-IV-TR criteria, it addresses many peripheral symptoms such as sensory over-responsibility and problematic behavior, which are thought to be important in practical support for PDD patients. Through these four scales, PARS not only covers core PDD symptoms but also covers a wide variety of peripheral symptoms. Each subscale and the overall scale showed an α coefficient greater than .70, which demonstrated sufficient internal consistency.

Correlation with the ADI-R clearly duplicated the correspondence relationships with DSM-IV stated above, demonstrating the convergent validity of PARS. Furthermore, the Sensitivity/Difficulty scale showed a correlation with the ADI-R's Restricted, Repetitive, and Stereotyped Patterns of Behavior domain. This might show that the limited interest or fixation on specific things or objects may be the root cause of peripheral symptoms included in the Sensitivity/Difficulty scale.

Through the ROC analysis of the ability of PARS to distinguish between PDD and non-PDD, PARS showed high discriminative power regardless of the intellectual capacity of the patient. The total score demonstrated a higher discriminative power than the subscores, similar to the case with the ADI-R (Lord et al., 1997) and ASQ (Berument et al., 1999). Considering its ease of implementation, PARS may be superior to the ADI-R or ADOS in terms of cost performance. Furthermore, the ROC analysis indicated that the selected cutoff value of PARS is relatively stable regardless of the intellectual capacity of the patient. The fact that a fixed cutoff level can be employed regardless of the nature of the interview subjects is considerably important in terms of convenience and utility in practical use.

One limitation of the study is that the interviewers were not completely blind to the probands' diagnosis. This factor might have a positive influence on the result of discriminative power analysis. Thus, the conclusion about our measurement technique's discriminative power is limited. However, it is unlikely that this problem systematically affects the result of our other analyses (i.e., factor analysis, reliability analysis, and correlation analysis), because the lack of blindness might uniformly raise the score of the PDD group and lower the score of the control group. Such uniform changes do not affect these kinds of analyses.

Finally, we discuss future issues. First, although this study examined the discriminative power of PARS in differentiating between PDD patients and the general population, there is a need to examine its discriminative power in other developmental disorders, such as attention deficit hyperactivity disorder, which shows somewhat similar symptoms to PDD (Hattori et al., 2006), or in other mental disorders, including schizophrenia, depression, and anxiety disorder, which often occur together with PDD. Second, the effectiveness of PARS in distinguishing subordinate diagnoses of PDD, which was not included among the objectives of this study, also needs to be considered. By appropriately combining the four subscales extracted in the factor analysis, PARS might be able to distinguish among subordinate diagnoses. We believe this is also an important issue with respect to the versatility of PARS. Third, an English version needs to be developed if PARS is to be used internationally. Currently, PARS is published in Japan and is being used by many clinical and research institutions (Yamada et al., 2007), but it cannot be used overseas as the Japanese version is the only one that exists. Since PARS is simpler than the ADI-R or ADOS and has sufficient reliability and validity, it can be an extremely useful instrument worldwide.

Acknowledgement

This study was supported by a grant from the Foundation for Children's Future.

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J Autism Dev Disord (2013) 43:395–403
DOI 10.1007/s10803-012-1578-9

ORIGINAL PAPER

Individuals with Asperger's Disorder Exhibit Difficulty in Switching Attention from a Local Level to a Global Level

Masatoshi Katagiri · Tetsuko Kasai · Yoko Kamio · Harumitsu Murohashi

Published online: 23 June 2012

Abstract The purpose of the present study was to determine whether individuals with Asperger's disorder exhibit difficulty in switching attention from a local level to a global level. Eleven participants with Asperger's disorder and 11 age- and gender-matched healthy controls performed a level-repetition switching task using Navon-type hierarchical stimuli. In both groups, level-repetition was beneficial at both levels. Furthermore, individuals with Asperger's disorder exhibited difficulty in switching attention from a local level to a global level compared to control individuals. These findings suggested that there is a problem with the inhibitory mechanism that influences the output of enhanced local visual processing in Asperger's disorder.

Keywords Asperger's disorder · Level-repetition · Switching · Global · Local

Introduction

Autism spectrum disorder (ASD) encompasses several different disorders that are characterized by significant social deficits, repetitive behaviors, and restricted interests (American Psychiatric Association 2000). ASD includes prototypic autistic disorder, Asperger's disorder, and pervasive developmental disorder-not otherwise specified (Akshoomoff 2005; DiCicco-Bloom et al. 2006). As demonstrated in the embedded figures task and the block design task, individuals with ASD exhibit strong local processing compared to typically developing (TD) individuals (Shah and Frith 1983, 1993; Jolliffe and Baron-Cohen 1997).

The superior local processing by individuals with ASD in visual tasks has been explained by two hypotheses. The "weak coherence" hypothesis stresses a detail-focused processing style (Happé and Frith 2006). The latest refinements of the weak coherence hypothesis emphasize the notion of reduced global integration of information (Happé and Booth 2008). The "enhanced perceptual functioning" hypothesis proposed that, in ASD, low-level perceptual processing was both superior and the default setting of perception (Mottron et al. 2006). The enhanced perceptual functioning hypothesis emphasizes that individuals with ASD do not have deficits in the processing of global aspects of information, but rather are characterized by enhanced low-level perceptual processing and are more locally oriented than non-ASD individuals.

The local processing in ASD has been investigated through the use of global/local tasks with Navon-type hierarchical stimuli (e.g., a large letter composed of small letters, Navon 1977). However, the results of previous studies using hierarchical stimuli have not always been consistent with regard to their findings on local processing (e.g., Wang et al. 2007). Plaisted et al. (1999) found that individuals with ASD showed a local advantage effect (more errors were made at the global level than at the local level) for an incongruent stimulus (Fig. 1, No. 3; the global

M. Katagiri (✉)
Department of Neuropsychiatry and Neuropsychology, Graduate School of Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan
e-mail: katagiri@las.u-toyama.ac.jp

M. Katagiri · Y. Kamio
Department of Child and Adolescent Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan

T. Kasai · H. Murohashi
Faculty of Education, Hokkaido University, Sapporo, Japan

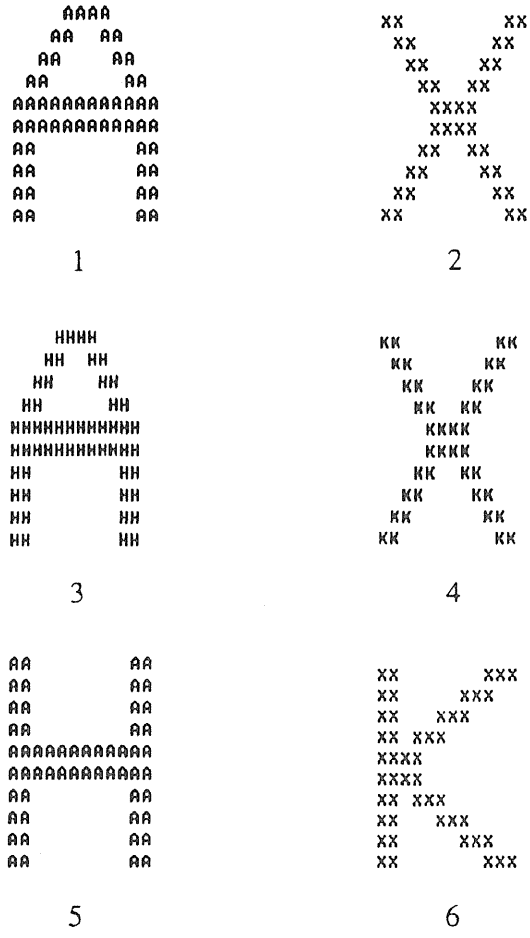

Fig. 1 Stimuli used in the divided-attention task (Plaisted et al. 1999)

and local levels are incongruent) in a divided-attention task. In the divided-attention task, the participant is required to identify a target stimulus (A) presented as either a large stimulus or small stimuli (Fig. 1). Thus, participants must attend to both the local level and the global level in each trial. Furthermore, participants must switch their attention between a global level and a local level with incongruent stimuli (Fig. 1, Nos. 3 and 5). Individuals with ASD may show enhanced local processing in the absence of priming and/or a deficit in switching attention to the global level, since participants were not told what level of attention they should focus on in anticipation of a stimulus.

Navon-type hierarchical stimuli seem to be effective for capturing local processing when used in open-ended tasks such as the divided-attention task (Happé and Frith 2006). This task is associated with an executive function. Rinehart et al. (2001) reported that individuals with ASD showed a slower response to a global target that appeared after a local target, compared to TD individuals. Thus, individuals with ASD exhibited difficulty in switching attention from a local level to a global level. In this experimental task, the participant must inhibit the global or local target, as appropriate, when they switch their attention to another level. It may be difficult for individuals with ASD to both switch their attention and inhibit the local target.

Incongruent Navon-type hierarchical stimuli incorporate a high level of interference between a global level and a local level. Rinehart et al. (2000) indicated that reaction times (RTs) in response to global-level stimuli are more strongly affected by incongruent stimuli at the local level in ASD. This study suggested that a local target disturbs the switching of attention from a local level to a global level; i.e., individuals with ASD showed local interference with a global target. When there is competition between the responses to a global target and a local target in incongruent stimuli, it may be difficult for individuals with ASD to inhibit the output of local visual processing in the absence of priming by instruction (Plaisted et al. 1999). In particular, executive dysfunction such as in switching and inhibition is associated with a problem in the cognitive flexibility. This cognitive ability has been examined with the use of the Wisconsin card sorting task, in which participants are required to inhibit a previous sorting rule and discover a new one (e.g., Geurts et al. 2009).

Previous studies using the divided-attention task with Navon-type hierarchical stimuli did not necessarily show local processing in individuals with ASD (Mottron et al. 2003; Ozonoff et al. 1994). There are at least three possible explanations for the inconsistent results in previous studies. First, the visual-perceptual processing between a global level and a local level may be sensitive to variations such as the quality of the information present at the global and local levels (goodness of form), or the number and relative sizes of the local elements (see Kimchi 1992, for a review). Second, difficulty in switching attention from a local level to a global level in ASD may be due to an inability to broaden the spread of visual attention towards a target in the periphery (Mann and Walker 2003). This dysfunction may be related to the executive dysfunction. Finally, difficulty in switching to a global target may be the result of a cognitive style characterized by detail-focused processing, such as in "weak coherence" (Happé and Frith 2006), or the superiority of enhanced low-level perceptual processing, such as in the "enhanced perceptual functioning" account (Mottron et al. 2006). The local processing may be related to a selective local inhibitory deficit. Most previous studies did not sufficiently examine these influences. Thus, previous studies have not clarified why individuals with ASD only exhibit difficulty in switching attention from a local level to a global level.

The purpose of the present study was to determine whether individuals with Asperger's disorder exhibit difficulty in switching attention. To achieve this goal, we used a level-repetition procedure that requires participants to enhance local or global visual-perceptual processing.

Furthermore, the goodness of form of a global configuration and a local element were carefully considered. As a novel experimental procedure, we used a level-repetition paradigm that involved switching trials and repetition trials. Hierarchical stimuli used in this paradigm were repeatedly presented at the same level, more than twice in a row, to provide additional focus on a global level or local level. In the level-repetition paradigm, RTs were reduced if the previous trial was at the same hierarchical level, but were increased if the previous trial was at a different level (e.g., Lamb and Yund 1996; Robertson 1996). The most noteworthy point is that the cost of switching is an effective means for capturing the effect of switching attention from a given perceptual level weighted by the level-repetition procedure.

We predicted that individuals with Asperger's disorder would exhibit the benefit of level-repetition at a local level. Due to the difficulty of inhibiting local-level stimuli in individuals with Asperger's disorder, the cost for switching attention from a local to global level is expected to be greater than that for global-to-local switching. If individuals with Asperger's disorder who show mild 'autistic' manifestations exhibit difficulty in switching attention from a local level to a global level, the results in the present study may provide important insights regarding local visual processing in ASD. To our knowledge, this is the first study to investigate the effect of level-repetition on switching using incongruent hierarchical stimuli in individuals with Asperger's disorder.

Methods

Participants

We examined 11 participants with Asperger's disorder (mean age = 31.1, *SD* = 6.13; 8 female, 3 male; mean full-scale IQ = 105, *SD* = 10.7, range 90–122) and 11 age- and gender-matched healthy controls (mean age = 28.3, *SD* = 5.35; 8 female, 3 male), who did not significantly differ in age (t (20) = 1.13, *n.s.*) and had no intellectual disability. All participants were right-handed and had normal or corrected-to-normal vision.

Participants with Asperger's disorder were recruited through the local Mental Health and Welfare Center. All of the participants had participated in a group psychotherapeutic intervention carried out at this center. Since many of the participants in the group intervention program were female, there were more female participants than males in this study.

All diagnoses of Asperger's disorder were established according to the DSM-IV-TR criteria for Asperger's disorder (American Psychiatric Association 2000) based on a series of clinical assessments that included an interview, information from each participant and childhood clinical records (developmental history, child psychiatric and psychological observations, and tests and neurologic investigations). The process used for the differential diagnosis of Asperger's disorder is described below. Clinical psychologists collected information from parents on developmental milestones (including joint attention, social interaction, pretend play and repetitive behaviors, with onset prior to age 3 years) and episodes (e.g., how the individual with Asperger's disorder behaved at kindergarten and school). The differential diagnosis of Asperger's disorder considered verbal communication and verbal development. Information about detailed observations of interactions with people (particularly non-family members) as well as repetitive behaviors, obsessive/compulsive traits, and stereotyped behaviors, was also provided by other professionals (teachers, social workers, etc.). For the assessment of IQ and neuropsychological characteristics, all participants with Asperger's disorder completed a Japanese version of the Wechsler Adult Intelligence Scales-third edition (WAIS-III). An expert psychiatrist interviewed each participant in the Asperger's disorder group at least three times (each on a separate day) before the final diagnosis was made. None of the participants in the Asperger's disorder group had other developmental or psychiatric disorders. Three of the 11 participants with Asperger's disorder were taking medications, but were free of these medications at the time of testing.

Control participants were recruited from among undergraduate and graduate university students. The IQ scores were not available for some participants in the control group who had previously learned about IQ assessments. They were required to be in good physical health, and were free of regular medication usage. An additional exclusion criterion for the healthy control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives.

Written informed consent was obtained for each participant before the test, according to the Declaration of Helsinki. The study protocol was approved in advance by the ethics committee.

Apparatus and Stimuli

This experiment was conducted in a soundproof chamber, to reduce distractions, using E-Prime software and a Serial Response-Box (Psychology Software Tools, Inc). In each trial, a hierarchical stimulus was presented on a 17-inch computer monitor. The viewing distance for each participant was approximately 57 cm. The hierarchical stimulus was a large digit (global) composed of smaller digits (local). Global 2s and 3s were always composed of local 4s

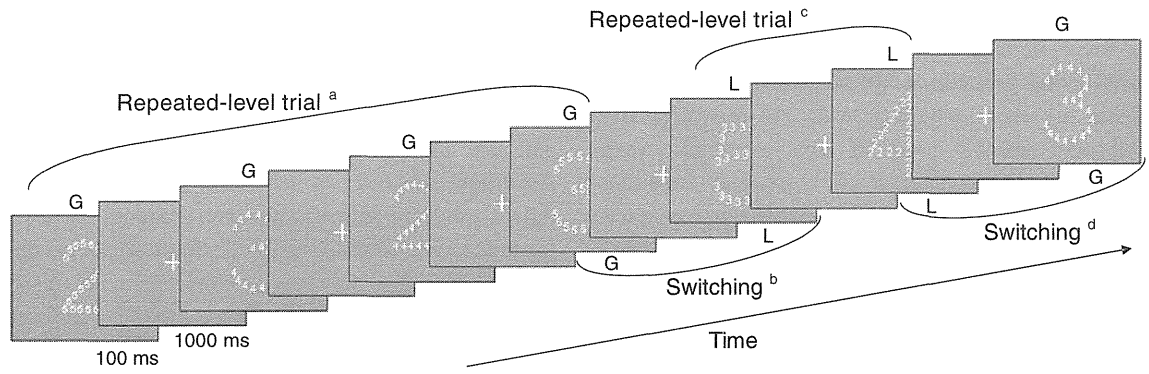

Fig. 2 Sequence of the experimental trials. The first repeated-level trial shows a switch after a four repeated-level trial, and the second shows a switch after a two repeated-level trial. *G* global-level target; *L* local-level target. *a* Four repeated-level trial (repetition of four global targets). *b* Global-to-local switching (switching from the global level to the local level after a four repeated-level trial). *c* Two repeated-level trial (repetition of two local targets). *d* Local-to-global switching (switching from the local level to the global level after a two repeated-level trial)

and 5s, whereas global 4s and 5s were always composed of local 2s and 3s. Thus, these were all incongruent stimuli composed of target (2 and 3) and distractor digits (4 and 5). Global stimuli subtended a visual angle of 3.7 in height and 2.5° in width, and local stimuli subtended 0.4° × 0.3°. All stimuli were displayed at the center of the monitor, and were drawn in white on a gray background (see Fig. 2).

Procedure

The experimental task was a divided-attention task that used a level-repetition procedure (Fig. 2). In the present study, the divided-attention task and stimuli were based on the study by Rinehart et al. (2001), and the level-repetition procedure was based on the study by Wilkinson et al. (2001). A fixation cross appeared for 1,000 ms, and the hierarchical stimulus was displayed for 100 ms. Participants were instructed to press the left button when a '2' appeared, and to press the right button when a '3' appeared, regardless of the level (global or local), as quickly and accurately as possible using the forefingers. There were six patterns of repeated-level trials: target repetition occurred either at the global level or local level, and the number of repetitions at the same target level was two, four, or five. Switching trials were defined as those that occurred between global and local repeated-level trials (see Fig. 2). Thus, in a switching trial, the target level switched from either global-to-local or local-to-global, and this was part of the next repeated-level trial. Participants completed two practice blocks (total 24 repeated-level trials). Further practice was provided on request. After the practice blocks, participants performed eight experimental blocks (total 192 repeated-level trials). Between blocks, they were allowed to rest for some time. A complete session took between 30 and 45 min.

Wilkinson et al. (2001) indicated that the RT taken to identify a target in a changed-level trial following four repeated-level trials was longer than that after two repeated-level trials. However, a changed-level trial following six repeated-level trials did not produce any additional increases beyond the RT with four. To shorten the total experimental time, we used two, four and five repeated-level trials. Although the target identity changed randomly, the hierarchical level at which the target appeared was strictly controlled. The sequence of trials was presented serially on the screen in a pseudorandom order with an equal probability for each target level (local, global), target digit (2, 3), distractor digit (4, 5), and trial condition (number of repetitions, switching).

Statistical Analyses

Error rates and RTs for the response to the preceding stimulus were analyzed in repeated-level trials and switching trials, respectively. These data were subjected to a mixed-design ANOVA. For repeated-level trials, the factors were group (Asperger's disorder group, control group) as the between-subject factor, and target level (global, local) and number of repetitions (two, three, four, five) as within-subject factors. For switching trials, the factors were group (Asperger's disorder group, control group) as a between-subject factor, and switching direction (global to local, local to global) and number of repetitions (two, four, five) as within-subject factors.

To more directly examine the switching-attention operations, we calculated the "switching cost" by subtracting RTs in repeated-level trials from those in switching trials. For example, the switching cost in the global-to-local direction after a four repeated-level trial for a global target was calculated as (RTs for a local target in switching trials) minus (RTs for the fifth global target in five repeated-level

trials). We calculated the cost for switching direction after two and four repetitions. Switching costs were statistically analyzed using three-way repeated measures ANOVA: group (Asperger's disorder group, control group) × switching direction (global to local, local to global) × switching cost in repetitions (two, four). In post hoc tests, multiple comparisons were performed using the Bonferroni test.

Results

Error Rate

Table 1 shows the mean error rates for repeated-level trials and switching trials. With regard to error rates in repeated-level trials, only the number of repetitions had a significant main effect (F (3, 60) = 6.96, $p < .001$), and in switching trials only the switching direction had a significant main effect (F (1, 20) = 8.98, $p < .01$). There were no other statistically significant effects. There was also no significant difference in the mean of all error rates between the Asperger's disorder group (6.33 %, SD = 8.4) and the control group (2.57 %, SD = 1.73) in an independent samples t test (t (20) = 1.45, $p = .16$).

Reaction Time

With regard to RTs in repeated-level trials, only the number of repetitions had a significant main effect (F (3, 60) = 17.69, $p < .001$). The main effects of group and target level were not significant [F (1, 20) = 3.74, $p = .068$; F (1, 20) = .48, $p = .50$, respectively] (Fig. 3).

With regard to switching trials, the only significant interaction was between the group and switching direction (F (1, 20) = 7.76, $p < .05$). Post hoc comparisons revealed that global-to-local switching generated longer latencies than local-to-global switching in the control group, and especially after two and five repetition-level trials [F (1, 20) = 5.62, $p < .05$; F (1, 20) = 11.19, $p < .01$, respectively]. This effect was insignificant for the Asperger's disorder group. None of the main effects or other interactions were significant (Fig. 4).

Switching Cost

A three-way ANOVA revealed that there was a significant main effect of switching cost in repetitions (F (1, 20) = 4.45, $p < .05$). Interestingly, there was a significant interaction between the switching direction and group (F (1, 20) = 6.63, $p < .05$). Post hoc comparisons revealed that the switching cost from the local level to the global level in both two and four repeated-level trials was higher

Table 1 Mean error rates (percentage) in repeated-level trials and switching trials

	Repeated-level trials									Switching trials					
	Global target				Local target					Two		Four		Five	
	Two	Three	Four	Five	Two	Three	Four	Five		G-L	L-G	G-L	L-G	G-L	L-G
AD (*SD*)	5.49 (7.13)	3.88 (5.39)	3.69 (4.64)	1.80 (2.42)	5.49 (7.17)	2.75 (2.96)	2.94 (3.45)	1.42 (2.05)		9.66 (14.22)	8.81 (14.17)	9.09 (11.04)	6.82 (15.74)	12.5 (20.82)	9.94 (15.49)
Control (*SD*)	1.89 (1.79)	0.66 (0.96)	1.33 (1.48)	0.76 (1.33)	1.42 (1.94)	1.33 (1.33)	1.70 (1.82)	0.66 (1.26)		5.94 (6.66)	2.19 (3.31)	6.56 (4.28)	4.38 (3.95)	6.25 (4.65)	4.69 (4.23)

Two, three, four and five indicate the number of preceding repetitions at the target level. G-L, direction of switching after repeated-level trials (global-to-local), L-G, target-switching from local to global levels

AD Asperger's disorder, *SD* standard deviation

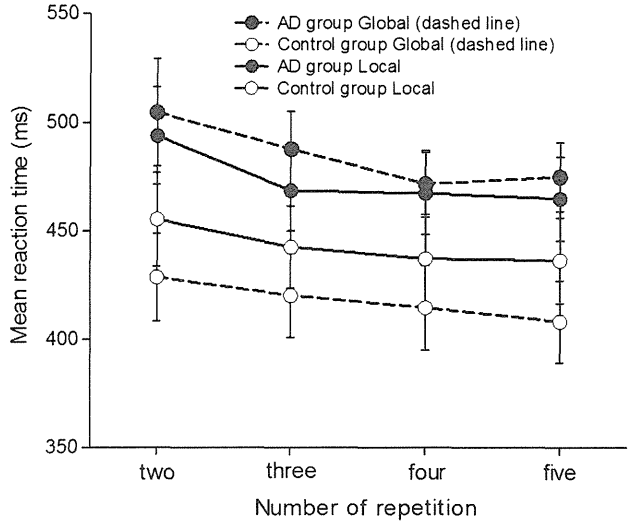

Fig. 3 Mean reaction times for repeated-level trials. *Bars* indicate the standard error of the mean. *AD* Asperger's disorder

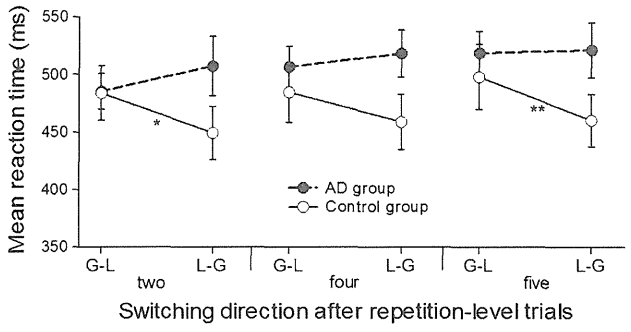

Fig. 4 Mean reaction times for switching trials. *G-L* indicates global-to-local switching after repeated-level trials, and *L-G* indicates local-to-global switching. *Two*, *four* and *five* indicate the number of repetitions in repeated-level trials. *Bars* indicate the standard error of the mean. *AD* Asperger's disorder. $^{**}p < .01$, $^{*}p < .05$

for the Asperger's disorder group than for the control group [F (1, 20) = 7.73, $p < .05$, F (1, 20) = 4.81, $p < .05$, respectively]. In the control group, the switching cost from the global level to the local level was greater than that for switching in the opposite direction in two repeated-level trials (F (1, 20) = 6.59, $p < .05$), while this difference was not significant in the Asperger's disorder group (two repeated-level trials: F (1, 20) = 3.29, $p = .085$) (Fig. 5).

Discussion

We predicted that individuals with Asperger's disorder would exhibit a benefit of level-repetition at a local level and a high cost when switching attention from a local to a global level. Our data yielded two main findings. First, although there were no statistically significant differences

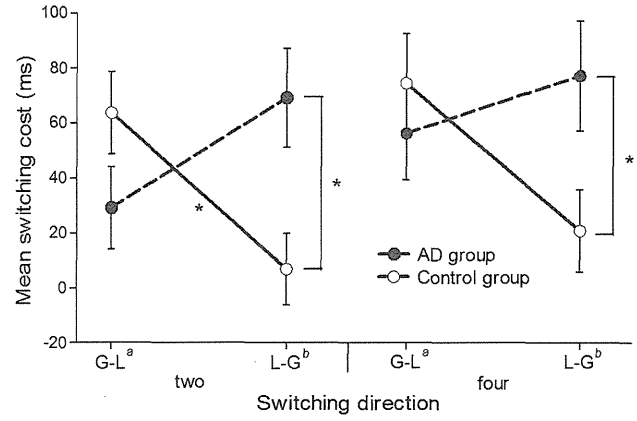

Fig. 5 Switching cost for switching trials. *G-L* indicates global-to-local switching after repeated-level trials, and *L-G* indicates local-to-global switching. *Two* and *four* indicate the number of repetitions in repeated-level trials. *Bars* indicate the standard error of the mean. *AD* Asperger's disorder; *L* Local target; *G* Global target. $^{*}p < .05$. *a* Switching cost of G-L was calculated as [RTs for a local target after repeated-level trials with a global target (two or four)] − (RTs for a global target after three or five repetitions with a global target). *b* Switching cost of L-G was calculated as [RTs for a global target after repeated-level trials with a local target (two or four)] − (RTs for a local target after three or five repetitions with a local target

in the mean of all error rates between the Asperger's disorder group and the control group, both groups exhibited a benefit of level-repetition at both levels. Second, the Asperger's disorder group exhibited greater costs, in terms of RT, when switching from a local target to a global target compared to the control group. Consequently, individuals with Asperger's disorder exhibited enhanced visual processing at both perceptual levels and difficulty in switching attention from a local level to a global level compared to control individuals. These results replicated the results of a previous study (Rinehart et al. 2001) and constitute evidence of impaired local switching in ASD.

Difficulty in Switching Attention from a Local Level to a Global Level

Based on the error rates observed in this study, both target levels and level-repetition trials and switching trials were accurately detected in both groups. This result is inconsistent with that of Plaisted et al. (1999), who found more errors in the incongruent/global condition. Based on the mean RTs for repeated-level trials, both groups exhibited a benefit of level-repetition at both levels. These results regarding error rates and RTs suggested that visual-perceptual processing in individuals with Asperger's disorder was intact, which is consistent with the "enhanced perceptual functioning" hypothesis (Mottron et al. 2006). In addition, they did not necessarily show executive dysfunction when switching attention, but had difficulty in

switching attention in the local-to-global direction. This finding is consistent with a selective deficit in broadening of the spread of visual attention in individuals with ASD (Mann and Walker 2003). These findings also suggested that local processing and global processing involve independent mechanisms (Happé and Booth 2008).

In the control group, RTs in switching from a global target to a local target were significantly longer than those in switching in the opposite direction but there were no significant differences in switching directions in the Asperger's disorder group. In addition, the control group showed greater switching costs upon going from a global level to a local level than when switching in the opposite direction. These results suggest that control individuals showed greater interference from the global level to the local level (global interference) and stronger global processing than individuals with Asperger's disorder. The findings in individuals with Asperger's disorder are also reflected in relatively enhanced local processing or attenuated global processing compared to control individuals.

Importantly, the results regarding the switching cost show that the Asperger's disorder group showed difficulty in switching attention from a local level to a global level compared to the control group. Thus, individuals with Asperger's disorder showed greater interference in switching from the local level to the global level (local interference). This finding suggested that it was difficult for individuals with Asperger's disorder to inhibit local visual-perceptual processing that was enhanced by the repetition procedure in the context of competition between the global level and the local level.

Assumed Mechanisms of Level-Repetition and Inhibition

In the present study, the switching cost in a four repeated-level trial was greater than that in a two repeated-level trial in both groups. Furthermore, in the control group, the switching cost from the global level to the local level was greater than that for switching in the opposite direction in two repeated-level trials. When the control group continuously attended to global targets, this may have increased the activity of global visual processing that is involved in the processing of global information. In contrast, when the Asperger's disorder group continuously attended to local targets, this may have increased the activity of local visual processing that is involved in the processing of local elements. Thus, the greater switching cost for each level suggests that control individuals were unable to inhibit target stimuli at the global level, while individuals with Asperger's disorder were unable to inhibit target stimuli at the local level.

The level-repetition effect results from the automatic activation of level-specific neural mechanisms (Lamb et al. 1998). This effect promotes the response to the same level and interferes with the response to a different level. The promotion of the reaction was enhanced by the repetition of an attentional level (Robertson 1996). In the present study, the control group showed low switching costs when they switched attention from a local target to a global target after a two repeated-level trial for a local target. This finding suggests that global processing in control individuals disappeared with attentional weighting in local level-repetitions. The properties of visual processing observed with Navon-type hierarchical stimuli can be explained by the relative levels of local and global visual processing (Plaisted et al. 1999). Local-level priming helped to enhance the saliency of local elements in individuals with Asperger's disorder. As a result, they were unable to filter out information at the local level, which supports the notion of Plaisted et al. (1999) that there is a problem in an inhibitory mechanism that influences the output of local visual processing. The problem with this inhibitory mechanism in individuals with Asperger's disorder may either produce a local bias or weaken a global bias. The notion of a selective local inhibitory deficit caused by enhanced local processing is consistent with the "enhanced perceptual functioning" hypothesis (Mottron et al. 2006), rather than the "weak coherence" hypothesis (Happé and Frith 2006).

Limitations and Future Research Directions

Several methodological limitations should be noted. In the present study, while the participants were matched for both age and gender; both the control and Asperger's groups had more females than males. This bias may affect our ability to generalize our findings. In addition, while the control group had no deficits in mental ability, IQ scores were not available. It is possible that some cognitive abilities may have influenced the switching patterns in the participants. The present study did not examine the development of global processing or local processing in each participant. A recent study on the developmental trajectory of global–local processing showed that individuals with ASD do not transition to a global processing bias, which appears to begin in adolescence in TD individuals (Scherf et al. 2008). Future longitudinal studies on the development of local processing in children with Asperger's disorder and TD children should help to establish the connections between local processing and deficits in the perception of social information. These studies may reveal that the social deficits in ASD underlie a failure to integrate local details into a global entity (Jarrold et al. 2000).

Importantly, the present study cannot directly indicate that the difficulty in switching attention from the local level to the global level is enhanced by repetitions at the local

level, due to the absence of no-repetition trials. Thus, although our findings are related to a processing deficit in individuals with Asperger's disorder, we cannot conclude whether the current findings reflect an enhanced local processing bias. Further research using both a cognitive task and observed behavior in individuals with ASD should investigate whether we can establish a relationship with everyday behavior (Geurts et al. 2009). The examination of atypical behaviors (such as repetitive behaviors and restricted interests) or some other unexplored possibilities may be useful for understanding the association between the difficulty in switching attention from a local level to a global level and social deficits, which could in turn provide insight into the development of clinical interventions in individuals with ASD.

Conclusions

In conclusion, individuals with Asperger's disorder and control individuals exhibited the benefit of level-repetition at both global and local levels. Furthermore, individuals with Asperger's disorder showed significantly greater costs (in terms of longer RTs) on switching from a local target to a global target. Consequently, individuals with Asperger's disorder exhibit difficulty in switching attention from a local level to a global level compared to control individuals. These results in individuals with Asperger's disorder who show mild 'autistic' manifestations may provide insight into local visual processing in ASD. This difficulty in switching attention suggested that there is a problem with the inhibitory mechanism that influences the output of enhanced local visual processing. A better understanding of the characteristics of local processing may contribute to clinical interventions in individuals with ASD. It is quite likely that our level-repetition switching task with incongruent hierarchical stimuli facilitated visual processing in each group, and more sensitively revealed a difficulty in switching attention.

Acknowledgments We would like to thank all of the participants for making this research possible. We would also like to thank Dr. Tsukishima and Dr. Nakano for their help. We are grateful to Ms. Numata, Ms. Watanabe, Ms. Uematsu and Dr. Matsui for their helpful and insightful comments on this article. This study was supported by the Japan Society for the Promotion of Science (no. 23730870).

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Review
Clinical Psychopharmacology and Neuroscience 2011;9(3):102-110
pISSN 1738-1088 / eISSN 2093-4327

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

Hidetoshi Takahashi[1,2], Ryota Hashimoto[2,3,4], Masao Iwase[2], Ryouhei Ishii[2], Yoko Kamio[1], Masatoshi Takeda[2]

[1]Department of Child and Adolescent Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, [2]Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, [3]CREST (Core Research for Evolutionary Science and Technology), JST (Japan Science and Technology Agency), Saitama, [4]Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, Osaka, Japan

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.

Received: September 20, 2011 / **Revised:** November 18, 2011
Accepted: November 21, 2011
Address for correspondence: Hidetoshi Takahashi, MD, PhD
Department of Child and Adolescent Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashicho, Kodaira, Tokyo 1878553, Japan
Tel: +81-42-341-2711, Fax: +81-42-346-1944
E-mail: htakahashi@ncnp.go.jp

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) α 3 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.

PPI IN CHILDREN AND DEVELOPMENTAL DISORDERS

Startle modulation is not consistent through children to adults. The neurophysiological mechanisms of PPI are considered to undergo development during early childhood and do not mature until about 8 years of age in both male and female subjects.[113,114]

Several studies have revealed PPI impairment in children with psychiatric disease, such as the 22q11 deletion syndrome,[115] Tourette's syndrome[116] and primary nocturnal enuresis.[117] On the other hand, children with autism,[118,119] attention deficit hyperactivity disorder (ADHD),[120,121] PTSD,[122] did not show PPI deficits (in traditional PPI experimental paradigm).

It should be noted that discrepancy in PPI between children and adults can be found in some psychiatric diseases. For instance, although children with autism did not[118,119] show PPI deficits, adults with ASD, such as autism[123] or Asperger's syndrome,[124] presented PPI impairments. Adults with PTSD also exhibited PPI deficits,[125,126] while children[122] or adolescent[127] with PTSD did not. The neurophysiological development related to PPI of startle response might not be relevant for some psychiatric diseases, such as ADHD, which did not exhibit PPI impairment in both children[120,121] and adults,[128,129] but might affect the discrepancy in PPI impairment between children and adults in other diseases, such as ASD or PTSD. Although PPI did not differ significantly between children with autism and normal age-matched controls, PPI of some controls were not evaluated, since they were rejected from the study for reasons such as drowsiness or small response.[119] Patients with autism are known to have hyperacusia, and they might present a lower threshold of startle and elicit startle by weak stimuli which might not elicit startle in normal controls. It is important to determine an experimental paradigm which can assess sensorimotor gating in both children with ASD and typical development. Although PPI impairment is not apparent in children with autism, there might be deficits in the mechanism of startle response in children with ASD which would develop to PPI impairment when they become adults, and comprehensive investigation of startle response, including threshold to elicit startle, startle magnitude, as well as PPI, might contribute to uncover the impairment of the neural circuitry in autism. There are several attempts to develop experimental paradigm of PPI,[114,130-135] including attentional modulation of PPI,[114,132-135] and application of these paradigms might inform neurobiological basis underpinning PPI deficits in both children and adults with ASD.

CONCLUSION

PPI is a well-established neurophysiological index for translational research in psychiatric diseases. Recent studies from a variety of research areas all over the world have provided us important evidence to understand the neural mechanisms of sensorimotor gating, assessed by PPI. These findings will be most valuable in devising future studies that aim at investigating and understanding the complex pathogenesis of psychiatric diseases.

Acknowledgments

The authors gratefully thank Dr. Young-Chul Chung for inviting us to publish this review and Dr. Antonio Currais for editorial review.

This work was supported in part by Grants-in-Aid from the Japanese Ministry of Health, Labor and Welfare (H18-kokoro-005, H19-kokoro-002), the Japanese Ministry of Education, Culture, Sports, Science and Technology (17591211, 18689030, 20591402, 21791130, 23890257), Intramural Research Grant (23-1) for Neurological and Psychiatric Disorders of NCNP, CREST of JST, Japan Foundation for Neuroscience and Mental Health, and Mitsubishi Pharma Research Foundation. The study sponsors had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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