both the consensus clinical diagnosis and the algorithm diagnosis. The caregivers were then provided with feedback, including a best-estimate diagnosis.

Results

Reliability Study

No single diagnostic algorithm item showed a weighted kappa (Kw) of lower than 0.6 (see Appendix Table 1 in supplementary materials). Two items showed Kw values at the level of "good" in terms of clinical significance (0.74 for item 39, "Verbal rituals", and 0.69 for item 58, "Inappropriate facial expression"), but the remaining 40 out of 42 diagnostic algorithm items showed Kw values of 0.75 or higher, indicating a level of excellent clinical significance.

All domains and subdomains showed ICC values of 0.75 or higher, indicating an excellent level (Table 3). ICC values were again calculated separately for three age bands (<5:0 years, 5:0–9:11 years, and 10–19 years). Among individuals below 5 years of age, all domains and subdomains had ICC values of ≥0.75 (excellent). For individuals between 5:0 and 9:11 years, all domains and all but one subdomain had ICC values of ≥0.75 (excellent); one exception was subdomain C3, "Stereotyped and repetitive motor mannerisms", which showed an ICC value of 0.73 (good). For those individuals 10 years of age and older, all domains and all but two subdomains showed ICC values of ≥0.75 (excellent); the exceptions were 0.69 for subdomain B2 (V), "Relative failure to initiate or sustain conversational interchange", and 0.62 for subdomain C4, "Preoccupations with part of objects or non-functional elements of material", which had ICC values over 0.6, but below 0.75 (good).

Validity Study

Discriminant Validity: Difference in Mean Scores of Items/Subdomains/Domains Across Three Diagnostic Groups

As regards the mean scores for diagnostic algorithm items (Table 4), all items but one showed a clear, significant difference across the three diagnostic groups using one-way ANOVA (AD vs. PDDNOS vs. non-ASD, $p < 0.001$

Table 3 Inter-rater reliability: intraclass correlation coefficients (ICC) of ADI-R domain and subdomain scores across three age bands (N = 51)

Domain/subdomain code	Item	ICC all subjects [N = 51]	ICC <5:0 years [N = 20]	ICC 5:0–9:11 years [N = 15]	ICC 10–19 years [N = 16]
A	Qualitative abnormalities in reciprocal social interaction	.96	.93	.97	.95
A1	Failure to use nonverbal behaviors to regulate social interaction	.92	.91	.94	.91
A2	Failure to develop peer relationships	.95	.92	.92	.90
A3	Lack of shared enjoyment	.96	.94	.98	.97
A4	Lack of socioemotional reciprocity	.91	.93	.89	.88
B	Qualitative abnormalities in communication	.97	.95	.96	.98
B1	Lack of, or delay in, spoken language and failure to compensate through gesture	.93	.94	.91	.92
B4	Lack of varied spontaneous make-believe or social imitative play	.96	.93	.97	.98
B2(V)	Relative failure to initiate or sustain conversational interchange	.92	.90	.92	.69
B3(V)	Stereotyped, repetitive, or idiosyncratic speech	.92	.96	.95	.77
C	Restricted, repetitive, stereotyped patterns of behaviour	.95	.96	.96	.87
C1	Encompassing preoccupation or circumscribed pattern of interest	.94	.97	.92	.81
C2	Apparently compulsive adherence to non-functional routines or rituals	.86	.85	.90	.81
C3	Stereotyped and repetitive motor mannerisms	.86	.85	.73	.96
C4	Preoccupations with part of objects or non-functional elements of material	.82	.89	.94	.62

Table 4 Discriminant validity: mean scores of diagnostic algorithm items, subdomains, and domains

Items	(1) AD [N = 138]	(2) PDDNOS [N = 89]	(3) Non-ASD [N = 90]	Statistics
A1. Failure to use nonverbal behaviors to regulate social interaction	3.8 (1.7)	2.6 (2.0)	0.2 (0.6)	$F(2, 314) = 138.4$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
50. Direct gaze	1.5 (0.9)	1.1 (1.0)	0.0 (0.3)	$F(2, 227) = 61.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.002$
51. Social smiling	1.9 (1.1)	1.4 (1.2)	0.1 (0.4)	$F(2, 230) = 60.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.01$
57. Range of facial expressions used to communicate	1.2 (1.0)	0.8 (1.0)	0.0 (0.1)	$F(2, 231) = 34.1$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.03$
A2. Failure to develop peer relationships	5.7 (1.9)	4.4 (2.1)	0.7 (1.1)	$F(2, 314) = 226.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
49. Imaginative play with peers	2.1 (0.9)	1.9 (1.0)	0.2 (0.6)	$F(2, 224) = 95.4$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
62. Interest in children	1.9 (1.1)	1.4 (1.1)	0.1 (0.4)	$F(2, 229) = 63.1$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.01$
63. Response to approaches of other children	1.3 (0.9)	1.1 (0.8)	0.1 (0.3)	$F(2, 226) = 50.25$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
64. Group play with peers	2.2 (0.8)	1.8 (0.9)	0.4 (0.7)	$F(2, 221) = 94.7$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
65. Friendships	1.6 (1.1)	1.7 (0.9)	0.2 (0.5)	$F(2, 139) = 19.4$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
A3. Lack of shared enjoyment	4.3 (1.7)	3.7 (1.8)	0.7 (1.2)	$F(2, 314) = 146.3$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.006$
52. Showing and directing attention	1.5 (1.2)	1.0 (1.1)	0.0 (0.3)	$F(2, 229) = 39.3$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.01$

Table 4 continued

Items	(1) AD [N = 138]	(2) PDDNOS [N = 89]	(3) Non-ASD [N = 90]	Statistics
53. Offering to share	2.0 (0.9)	1.7 (1.1)	0.2 (0.5)	$F(2, 227) = 75.4$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
54. Seeking to share enjoyment with others	1.4 (0.7)	1.2 (0.8)	0.1 (0.3)	$F(2, 229) = 81.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
A4. Lack of socioemotional reciprocity	6.0 (2.1)	4.3 (2.2)	0.7 (1.1)	$F(2, 314) = 226.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
31. Use of other's body to communicate	1.0 (1.2)	0.8 (1.0)	0.2 (0.5)	$F(2, 273) = 226.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
55. Offering comfort	2.1 (1.1)	1.7 (1.3)	0.0 (0.2)	$F(2, 231) = 76.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS
56. Quality of social overtures	1.7 (1.2)	1.2 (1.1)	0.1 (0.2)	$F(2, 225) = 49.9$, $p < 0.001$ 1 > 3: p < 0.001 2 > 3: $p < 0.001$ 1 > 2: $p = 0.02$
58. Inappropriate facial expression	0.9 (0.8)	0.4 (0.6)	0.0 (0.3)	$F(2, 293) = 48.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
59. Appropriateness of social responses	1.7 (1.1)	1.4 (1.2)	0.2 (0.6)	$F(2, 227) = 47.1$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
A. Quantitative abnormalities in eciprocal social interaction	19.9 (5.3)	14.8 (6.4)	2.3 (2.7)	$F(2, 314) = 330.6$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
B1. Lack of, or delay in, spoken language and failure to compensate through gesture	4.1 (2.5)	3.0 (2.2)	0.6 (1.2)	$F(2, 314) = 79.1$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
42. Pointing to express interest	1.2 (0.9)	0.9 (0.9)	0.1 (0.4)	$F(2, 227) = 38.4$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: NS

Table 4 continued

Items	(1) AD [N = 138]	(2) PDDNOS [N = 89]	(3) Non-ASD [N = 90]	Statistics
43. Nodding	0.9 (0.8)	0.4 (0.6)	0.0 (0.2)	$F(2, 314) = 33.8$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.01$ 1 > 2: $p < 0.001$
44. Head shaking	0.8 (0.9)	0.5 (0.8)	0.1 (0.2)	$F(2, 224) = 21.3$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.003$ 1 > 2: $p = 0.03$
45. Conventional/instrumental gesture	1.4 (1.0)	0.9 (1.0)	0.1 (0.3)	$F(2, 228) = 41.7$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.002$
B4. Lack of varied spontaneous make-believe or social imitative play	4.2 (1.8)	2.8 (2.0)	0.6 (1.1)	$F(2, 314) = 124.9$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
47. Spontaneous imitation of actions	2.2 (1.1)	1.7 (1.2)	0.2 (0.6)	$F(2, 314) = 72.0$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
48. Imaginative play	2.0 (1.1)	1.5 (1.1)	0.2 (0.6)	$F(2, 227) = 124.9$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.004$
61. Imitative social play	1.5 (0.9)	1.1 (1.0)	0.0 (0.1)	$F(2, 226) = 53.9$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.003$
B2(V). Relative failure to initiate or sustain conversational interchange	3.1 (1.3)	1.9 (1.6)	0.5 (1.1)	$F(2, 307) = 97.9$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
34. Social verbalization/chat	1.7 (0.6)	1.4 (0.8)	0.5 (0.7)	$F(2, 314) = 67.5$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.01$
35. Reciprocal conversation	1.8 (0.7)	1.4 (0.8)	0.2 (0.6)	$F(2, 242) = 112.6$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.005$
B3(V). Stereotyped, repetitive, or idiosyncratic speech	2.9 (1.8)	2.1 (1.8)	0.9 (1.3)	$F(2, 314) = 41.2$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p = 0.004$
33. Stereotyped utterances and delayed echolalia	1.1 (1.1)	0.6 (0.8)	0.1 (0.4)	$F(2, 257) = 30.2$, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.008$ 1 > 2: $p < 0.001$

Table 4 continued

Items	(1) AD [N = 138]	(2) PDDNOS [N = 89]	(3) Non-ASD [N = 90]	Statistics
36. Inappropriate questions or statements	1.2 (0.8)	0.6 (0.7)	0.3 (0.5)	F(2, 258) = 45.7, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.02$ 1 > 2: $p < 0.001$
37. Pronominal reversal	0.3 (0.7)	0.1 (0.4)	0.2 (0.5)	F(2, 221) = 2.0, $p = 0.13$ NS
38. Neologisms/idiosyncratic language	0.4 (0.7)	0.2 (0.4)	0.2 (0.4)	F(2, 257) = 5.9, $p = 0.003$ 1 > 3: $p = 0.02$ 2 > 3: NS 1 > 2: $p = 0.01$
BV. Qualitative abnormalities in communications, verbal subjects	14.3 (4.1)	9.7 (4.4)	2.5 (3.2)	F(2, 260) = 210.9, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
BNV. Qualitative abnormalities in communications, non-verbal subjects	12.6 (4.9)	9.0 (4.4)	2.3 (2.5)	F(2, 51) = 21.0, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.005$ 1 > 2: $p = 0.02$
C1. Encompassing preoccupation or circumscribed pattern of interest	1.9 (1.1)	0.9 (1.0)	0.3 (0.6)	F(2, 314) = 80.6, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
67. Unusual preoccupation	1.0 (0.9)	0.4 (0.7)	0.1 (0.3)	F(2, 303) = 40.3, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.006$ 1 > 2: $p < 0.001$
68. Circumscribed interest	1.1 (0.8)	0.5 (0.7)	0.2 (0.5)	F(2, 294) = 40.5, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
C2. Apparently compulsive adherence to non-functional routines or rituals	1.4 (1.2)	0.7 (1.1)	0.2 (0.6)	F(2, 314) = 36.3, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.01$ 1 > 2: $p < 0.001$
39. Verbal rituals	0.8 (0.9)	0.4 (0.7)	0.1 (0.3)	F(2, 314) = 20.6, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.03$ 1 > 2: $p = 0.004$
70. Compulsions/rituals	0.9 (1.0)	0.5 (0.9)	0.2 (0.5)	F(2, 302) = 18.1, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: NS 1 > 2: $p = 0.002$
C3. Stereotyped and repetitive motor mannerisms	0.9 (0.9)	0.5 (0.8)	0.2 (0.6)	F(2, 314) = 19.4, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.03$ 1 > 2: $p = 0.03$

Table 4 continued

Items	(1) AD [N = 138]	(2) PDDNOS [N = 89]	(3) Non-ASD [N = 90]	Statistics
77. Hand and finger mannerisms	0.4 (0.7)	0.2 (0.5)	0.1 (0.4)	F(2, 302) = 9.6, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: NS 1 > 2: $p = 0.004$
78. Other complex mannerisms or stereotyped body movements	0.8 (0.9)	0.4 (0.7)	0.1 (0.4)	F(2, 303) = 21.5, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.04$ 1 > 2: $p = 0.001$
C4. Preoccupations with part of objects or non-functional elements of material	1.4 (0.7)	0.8 (0.7)	0.3 (0.6)	F(2, 314) = 66.5, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$
69. Repetitive use of objects or interest in parts of objects	1.2 (0.9)	0.5 (0.7)	0.2 (0.4)	F(2, 303) = 59.1, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.006$ 1 > 2: $p < 0.001$
71. Unusual sensory interests	0.7 (0.7)	0.5 (0.6)	0.2 (0.5)	F(2, 301) = 21.7, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p = 0.006$ 1 > 2: $p = 0.006$
C. Restricted, repetitive, and stereotyped patterns of behaviors	5.5 (2.4)	2.9 (2.5)	1.1 (1.8)	F(2, 314) = 106.6, $p < 0.001$ 1 > 3: $p < 0.001$ 2 > 3: $p < 0.001$ 1 > 2: $p < 0.001$

NS not significant

for all items, F test); the only exception was "Pronominal reversal (item 37)" ($p = 0.13$). For the post hoc analysis, the mean scores for all items, except item 37, differed significantly between the AD and non-ASD groups. In addition, the mean scores for all items differed significantly between the PDDNOS and the non-ASD groups, with the exception of "Neologism (item 38)" ($p = 0.87$, post hoc test with Bonferroni correction); "Compulsions (item 70)" ($p = 0.15$, post hoc test with Bonferroni correction); and "Hand and finger mannerisms (item 77)" ($p = 0.22$, post hoc test with Bonferroni correction).

As regards the subdomains (A1–A4, B1–B4, C1–C4), all showed a significant difference in mean scores across the three diagnostic groups using one-way ANOVA (AD vs. PDDNOS vs. non-ASD; $p < 0.001$ for all subdomains, F test; Table 4). For the post hoc analyses, the mean of all subdomain scores revealed a significant difference between the AD and non-ASD, PDDNOS and non-ASD, and AD and PDDNOS groups.

As for domains A, B (BV/BNV), and C, the mean scores for all 3 domains were significantly different across the three diagnostic groups with one-way ANOVA (AD vs. PDDNOS vs. non-ASD; $p < 0.001$ for all domains, F test; Table 4). For the post hoc analysis, the mean scores for all domains were significantly higher in the AD than in the non-ASD group ($p < 0.001$ for domains A, BV, BNV, and C, post hoc test with Bonferroni correction), and were higher in the PDDNOS than in the non-ASD group ($p < 0.001$ for domains A, BV, and C, $p = 0.005$ for domain BNV, post hoc test with Bonferroni correction). Likewise, the mean scores of all domains were significantly higher in the AD than in the PDDNOS group ($p < 0.001$ for domains A, BV, and C, $p = 0.02$ for domain BNV, post hoc test with Bonferroni correction).

Similar comparisons of mean scores of the three domains were repeated after stratification according to three age bands (<5:0 years, 5:0–9:11 years, and 10–19 years; see Appendix Table 3 in supplementary materials). For those individuals below 5 years of age, the mean scores for all domains were significantly higher in the AD (N = 11) than in the non-ASD group (N = 45)($p < 0.001$ for domain A, $p = 0.01$ for domain

BV, $p < 0.001$ for domain BNV, $p = 0.002$ for domain C, post hoc test with Bonferroni correction), and significantly higher in the PDDNOS (N = 33) than in the non-ASD group ($p < 0.001$ for domain A and BV, $p = 0.005$ for domain BNV, $p = 0.03$ for domain C, post hoc test with Bonferroni correction). However, no significant difference was found between the AD and PDDNOS groups in any of the domains ($p = 0.19$ for domain A, $p = 0.93$ for domain BV, $p = 0.33$ for domain BNV, $p = 0.29$ for domain C, post hoc test with Bonferroni correction). As for those individuals aged 5:0–9:11 years, the mean scores of all domains (A, BV, and C; note that no group comparison was conducted in domain BNV, because there was only one nonverbal subject in the non-ASD group in this age band) were significantly higher in the AD (N = 37) than in the non-ASD group (N = 28) ($p < 0.001$ for domains A, BV, and C, post hoc test with Bonferroni correction), and were significantly higher in the PDDNOS (N = 22) than in the non-ASD group ($p < 0.001$ for domains A, BV, and C, post hoc test with Bonferroni correction). Similarly, the mean scores for all three domains were significantly higher in the AD than in the PDDNOS group ($p = 0.01$ for domains A and C, $p = 0.03$ for domain BV, post hoc test with Bonferroni correction). As for those individuals aged 10–19 years, the mean scores for all three domains (A, BV, and C; no group comparison was conducted in domain BNV, because there was only one nonverbal subject in the non-ASD group in this age band) were significantly higher in the AD (N = 90) than in the non-ASD group (N = 17) ($p < 0.001$ for domains A, BV, and C, post hoc test with Bonferroni correction). Likewise, the mean scores for all domains except domain C were higher in the PDDNOS (N = 34) and non-ASD groups ($p < 0.001$ for domains A and BV, $p = 0.07$ for domain C, post hoc test with Bonferroni correction); moreover, for all domains, mean scores were also higher in the AD than in the PDDNOS group ($p = 0.002$ for domain A, $p < 0.001$ for domain BV and C, post hoc test with Bonferroni correction).

Again, the same analyses were conducted over two groups of IQ/DQ level (<70 vs. ≥70; see Appendix Table 4 in supplementary materials). For those individuals with an IQ/DQ of <70, the mean scores for all domains (A, BV/BNV, and C) were significantly higher in the AD (N = 18) than in the non-ASD (N = 8) group ($p < 0.001$ for domains A and C, $p = 0.007$ for domain BV and $p = 0.05$ for domain BNV, post hoc test with Bonferroni correction). The mean scores for domains A and BV were significantly higher in the PDDNOS (N = 9) than in the non-ASD group (N = 8), but no significant difference was found for domains BNV, and C ($p < 0.001$ for domain A, $p = 0.05$ for domain BV, $p = 0.13$ for domain BNV, $p = 0.99$ for domain C, post hoc test with Bonferroni correction). A significant difference in mean scores between the AD and PDDNOS groups was found only in domain C ($p = 0.99$ for domain A, $p = 0.08$ for domain BV, $p = 0.99$ for domain BNV, $p < 0.001$ for domain C, post hoc test with Bonferroni correction). In turn, for those individuals with an IQ/DQ of ≥70, mean scores for all domains were significantly higher in the AD (N = 120) than in the non-ASD group (N = 82) ($p < 0.001$ for domains A, BV, BNV, and C, post hoc test with Bonferroni correction), higher in the PDDNOS (N = 80) than in the non-ASD group ($p < 0.001$ for domains A, BV, C, $p = 0.002$ for domain BNV, post hoc test with Bonferroni correction), and higher in the AD than in the PDDNOS group ($p < 0.001$ for domains A, BV, C, $p = 0.01$ for domain BNV, post hoc test with Bonferroni correction).

Diagnostic Validity: Agreement with Consensus Clinical Diagnosis of AD

In our analysis of the overall diagnostic validity of the Japanese version of ADI-R, we found that across all individuals, the sensitivity, specificity, PPV, and NPV of the test were very high (92, 89, 87, and 93 %, respectively; Table 5). Similar results were also obtained for age groups 5:0–9:11 years and

Table 5 Diagnostic validity: agreement with consensus clinical diagnosis among those with algorithm diagnosis of AD

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Consensus clinical diagnosis: *Autistic disorder* [N = 138]				
Algorithm diagnosis of AD: Domain A ≥ 10 AND (Domain BV ≥ 8 for verbal OR BNV ≥ 7 for non-verbal subjects) AND Domain C ≥ 3 AND Domain D ≥ 1 (Rutter et al. 2003)				
All individuals [N = 317]	92	89	87	93
Age: below 4:0 [N = 73]	53	92	55	92
Age: below 5:0 [N = 89]	55	92	50	93
Age: 5:0–9:11 [N = 87]	92	84	81	93
Age: 10:0 and older [N = 141]	97	90	95	94
IQ/DQ: below 70 [N = 35]	94	100	100	94
IQ/DQ: 70 and over [N = 282]	92	88	85	93

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)

older, and for IQ/DQ groupings below 70 and at 70 and above. Consistent with our initial hypotheses, the sensitivity and PPV for ages below 4 and below 5 years were both poor, i.e., between 50 and 55 %, respectively.

Overall test sensitivity, or the proportion of individuals with AD (N = 138) who were correctly categorized as having AD using ADI-R-JV, was as high as 92 %, indicating excellent clinical significance, which was also shown for the evaluation of individuals aged 5:0–9:11 and age 10 years and older, and for those individuals at either cognitive level assessed, i.e., with a score of <70 or ≥70. However, for individuals aged below 5 years, a sensitivity of 55 % was found, indicating a poor level of clinical significance.

On the other hand, among individuals without a consensus clinical diagnosis of AD (N = 179), 159 were also judged not to have AD based on ADI-R-JV algorithm diagnosis, i.e., the specificity of ADI-R-JV for correctly excluding AD was 89 % (159/179), indicating excellent clinical significance. This clinically excellent specificity was replicated for individuals in each of the three age bands, and for both IQ/DQ bands examined.

Discussion

In the present study, we reported the inter-rater reliability, discriminant validity, and diagnostic validity of the Japanese Version of ADI-R (ADI-R-JV).

Reliability of ADI-R-JV

In agreement with our hypotheses, the Kw values for all algorithm items of ADI-R-JV exceeded a value of 0.6, which was also consistent with the findings of previous studies (Hill et al. 2001; Lord et al. 1994). Furthermore, among the 42 algorithm items, all but two (items 39 and 58) showed Kw values in excess of 0.75, indicating excellent inter-rater reliability; the two exceptions showed Kw values of 0.60–0.75, indicating good inter-rater reliability.

We also investigated whether the measures for inter-rater reliability would decrease when the analysis was limited to individuals in specific age bands (Table 3). Again, the ICCs for all domains and subdomains exceeded 0.75 (excellent) among individuals aged less than 5 years, and the ICCs for all but 1 (C3) subdomain exceeded 0.75 (excellent) among individuals aged 5:0–9:11 years. Of note, ICCs can be seen as reflecting a good to excellent level of clinical significance, regardless of the age of the examinee. It is worth mentioning in this context that the ICCs became smaller in subdomains B2(V), B3(V), C1, C2, and C4 if the examinees were 10 years old or older. This tendency, i.e., smaller ICC values of the age band of 10 years and older, should first be discussed in light of the definition of inter-rater reliability, which can be easily compromised when the degree of experience and training of pairs conducting the interviews differs. When such a difference in experience occurred in the present study, compromised ICCs should have been observed irrespective of a subject's age, since the two raters were selected on a random basis from each site. Furthermore, the raters who administered ADI-R-JV were fully and equally experienced after the official training sessions. Therefore, the compromised ICCs for those subjects 10 years old and older did not seem to reflect a bias stemming from assessment skills. There is agreement between our findings and previous results showing lower scores for items under domain C than for items under domains A and B (Hill et al. 2001; Lord et al. 1994). Specifically, the inter-rater reliability of items under domain C would be particularly likely to be compromised when the examinees were older (i.e., 10 years and older), probably due to the uncertain recall of remote episodes. However, since we only obtained limited findings regarding inter-rater reliability upon assessment of adolescent subjects, elaboration on this topic remains difficult.

On the other hand, ICCs were not lower when the analysis was limited to the examination of individuals with an intellectual disability (IQ/DQ < 70), or when only males or females were included in the analysis (Table not shown). Rather, under no circumstances did we observe a Kw or ICC below 0.6 (Table 3). These findings strongly indicate the satisfactory inter-rater reliability of ADI-R-JV, i.e., the translated version appears to be as reliable as the original ADI-R in English.

Validity of ADI-R-JV

Discriminant Validity

Mean scores for three domains (A, B[BV/BNV], and C) were significantly higher in the AD group than in the PDDNOS and the non-ASD groups, indicating that the discriminant validity of ADI-R-JV was stable. Thus, our results appear to be consistent with the findings of previous pivotal studies investigating younger individuals with AD (Lord et al. 1993; Saemundsen et al. 2003), even in those with concomitant developmental delay (Gray et al. 2008).

Originally, ADI-R was designed to detect AD, not ASD (Lord et al. 1994). Therefore, in the current analysis, we expected not only that the mean scores for all domains would be higher in the AD group than in the non-ASD group, but also that they would be higher in the AD than in the PDDNOS group. These two hypotheses held true when the analysis included all study participants (N = 317).

However, the latter hypothesis (mean scores for AD > mean scores for PDDNOS) did not hold true when the analysis was limited to individuals less than 5 years of age (Appendix Table 3 in supplementary materials). Presumably, one of the main reasons for the compromised discriminability (i.e., no difference between AD and PDDNOS reflected in ADI-R-JV scores for younger individuals) was that it is difficult to differentiate AD from PDDNOS in individuals younger than 5 years of age (Turner and Stone 2007). On the other hand, the present finding may also have been due to biases; for instance, the diagnostic algorithms were prepared separately for those aged 4 years and older (based on current and past behavior) and for those younger than 4 years of age (based on current behavior). Thus, it would be possible that the discriminant validity would differ for individuals younger than 4 years old and for individuals between 4 and 5 years old. We thus analyzed a restricted sample of individuals below 4 years of age (N = 73), and found that the mean scores for domain A were 14.5 for AD, 11.4 for PDDNOS, and 3.1 for non-ASD. These results indicated that the mean was slightly higher in the AD group than in the PDDNOS group ($p = 0.051$, after Bonferroni correction), whereas the mean scores for domain BV/BNV and domain C did not reveal such differences between the AD and PDDNOS groups, suggesting that the choice of algorithm according to age may have at least partly affected the results for younger individuals.

As regards to the above results stratified by age, attention should be paid to our sample selection; among individuals below 5 years of age, 12 % had AD and 33 % had PDDNOS, whereas 64 % had AD and 24 % had PDDNOS among individuals who were 10 years old or older. These figures are consistent with differences in mean age across the three diagnostic groups shown in Table 2, and that a sample bias influenced the results. If we were to have recruited younger children with AD in the analysis, a higher level of discrimination among subgroups would likely have been observed.

Discriminant validity was also compromised for individuals with an intellectual disability (IQ/DQ < 70, see Appendix Table 4 in supplementary materials). Again, we expected that the mean scores for all domains were higher in the AD group than in both the non-ASD and PDDNOS groups. The first hypothesis (mean scores for AD > mean scores for non-ASD) held true for all domains, regardless of IQ level. However, the second hypothesis (mean scores for AD > mean scores for PDDNOS) held true only for domain C among individuals with an IQ/DQ of < 70; instead, the relationship of mean scores for PDDNOS > mean scores for non-ASD was not observed for domain C among individuals with an IQ/DQ of < 70. These results suggest that the relevance of domain C in arriving at a diagnosis of AD may differ from the relevance of domains A and B, particularly for individuals with a developmental delay. This issue has already been addressed in the literature; some authors have argued that the exclusion of domain C may improve discriminability between toddlers with and without ASD (Ventola et al. 2006). Furthermore, Lord and Jones (2012) reviewed that compared to symptoms under the social interaction and communication domains, symptoms under the repetitive behavior domain (domain C) are more heterogeneous across individuals and context-dependent, and thus caregivers may not consistently notify clinicians about domain-C symptoms. Our findings appear to be in line with the results of these previous studies. Specifically, individuals with a consensus diagnosis of AD with concomitant cognitive delay would be diagnosed as having Social Communication Disorder according to the proposed version in the DSM-5 (http://www.dsm5.org/ProposedRevision/Pages/NeurodevelopmentalDisorders.aspx), using ADI-R-JV. This issue still needs to be addressed in future studies.

Thus far, the overall discriminant validity of ADI-R-JV has been shown to be sufficient, although it appeared compromised for the assessment of younger individuals and individuals with concomitant cognitive delay. Potential biases and the limited statistical power of the present study should be noted, as these factors might have resulted in the finding of compromised discriminability among younger individuals.

As shown in Table 4, "Pronominal reversal (item 37)" showed no statistical difference among the three diagnostic groups. This finding was of interest in terms of language use, because in Japanese conversations, personal pronouns are not as frequently used as they are in English. In addition, even when personal pronouns are not used, there are no verbal conjugations in Japanese that correspond to those in Latin-derived languages. We are certain that this specific feature of the Japanese language allowed the mean scores on item 37 to remain fairly close to zero. Nevertheless, this concern did not in any way affect discriminability among domain scores, nor was diagnostic validity affected.

Diagnostic Validity

The sensitivity of ADI-R-JV with respect to correctly diagnosing autistic disorder was 92 %, indicating that the overall sensitivity of the instrument is excellent. Moreover, the algorithm's overall specificity, which was shown to be 89 %, was determined to be good. Likewise, the overall PPV and NPV were 89 and 93 %, respectively, indicating good to excellent clinical significance, consistent with our expectations. These figures were similar or even better than those obtained in a recent study using a translated version of ADI-R administered to individuals with a mean age of 10 years (Lampi et al. 2010). However, in the current study, the corresponding sensitivity decreased to 55 % (indicating

poor sensitivity; Table 5) when the analysis was limited to subjects younger than 5 years of age, suggesting that diagnostic validity was compromised in younger individuals. This finding was also consistent with our hypothesis. The compromised sensitivity for younger individuals may be rather straightforward; prior studies have been consistent with this finding, and our own results indicated compromised discriminability between AD and PDDNOS individuals below 5 years of age. However, as such compromised discriminability was not firmly upheld due to potential biases and the limited statistical power of our study sample, analysis of a larger number of individuals may have provided a higher level of sensitivity. Indeed, a recent large-scale study indicated a sensitivity for correctly diagnosing AD as high as 82.7 %, even when participants were under the age of 36 months (Risi et al. 2006). Nevertheless, it remains possible that the low level of sensitivity for those aged less than 5 years in the present study was not simply due to sample selection or the algorithm applied, but also a reflection of the difficulty of differentiating AD from PDDNOS in individuals at such young age, as was suggested by recent literature (Turner and Stone 2007).

In light of the proposed diagnosis of ASD in the forthcoming Diagnostic and Statistical Manual of Mental Disorders (version 5), research interests have increasingly focused on differentiating ASD from non-ASD individuals using ADI-R; however, there is no established cutoff for ASD in ADI-R. Attempts have been made to apply the original algorithm to ASD individuals; unfortunately, sensitivity for correctly diagnosing ASD was shown to be insufficient (Kim and Lord 2012; Risi et al. 2006). A related attempt to differentiate ASD from non-ASD individuals using ADI-R was the use of other assessment scales such as the Vineland Adaptive Behavior Scale (Sparrow et al. 1984) to improve sensitivity (Tomanik et al. 2007). Another attempt at differentiation was to relax the original, stringent algorithm for AD. For instance, in one genetic study (International Molecular Genetic Study of Autism Consortium 2001), the diagnosis of ASD was made according to ADI-R, whereby exceeding the cutoffs of three domains (A, B, C) was required for ASD diagnosis, with the exception that a score on any one of the three domains could fall one point below the threshold. We recalculated sensitivity using this relaxed criterion in the current study, resulting in an overall sensitivity of 64 %. When the same analysis was repeated for three age bands, sensitivity was 27 % for subjects aged < 5 years old, 71 % for subjects aged 5:0–9:11 years old, and 74 % for those 10 years old and older (Table not shown). At present, ADI-R-JV appears to have limited diagnostic validity with respect to detecting ASD.

Nevertheless, studies have emphasized that the use of ADOS together with ADI-R is a sensible approach, in that the combination of the two reflects consensus clinical judgments of AD as well as of ASD better than any other single instrument used alone (Le Couteur et al. 2008), even in individuals as young as 3 years old and younger (Risi et al. 2006). In this regard, evaluations of the sensitivity of both the Japanese version of ADOS and ADI-R-JV for correctly diagnosing ASD should be conducted.

It should also be noted that the sensitivity of ADI-R-JV with respect to correctly diagnosing AD among individuals with concomitant cognitive delay (IQ/DQ < 70) was 94 %, i.e., not lower than the corresponding result for individuals with an IQ of >70 (92 %); this findings was inconsistent with our expectations, as well as with a prior study (de Bildt et al. 2004). Furthermore, other studies have shown that specificity was more prone than sensitivity to be compromised when the examinee exhibited cognitive delay, and thus individuals with cognitive delay are more likely to be overdiagnosed (Lord et al. 1994; Risi et al. 2006). As regards the discrepancy with our hypothesis, the sample bias of the present study should be taken into account, because the mean IQ/DQ of individuals with AD and PDDNOS in this study was fairly high, even higher than reported in previous studies. In addition, the small number of enrolled participants with an IQ/DQ of <70 could have limited the statistical power of the study to detect any compromising effects of cognitive delay on diagnostic validity.

Limitations and Strengths

Treatment or interventions that may have affected the children enrolled in this study should also be taken into account, particularly in the assessment of diagnostic subgroups. It was a limitation of this study that we did not collect relevant data on this topic. On the other hand, ADI-R is a measure based principally on the observation of past behavior during early stages of development, and usually is employed prior to such interventions, and is not based on a patient's current status. This means that the scores we obtained were less likely to reflect intervention effects compared to the scores of instruments that assess current behaviors, such as ADOS. In addition, we observed good to excellent inter-rater reliability, discriminant validity, and diagnostic validity of ADI-R-JV even without considering treatment effects that would have been observed among clinically referred individuals. Considering that statistical tests are generally biased toward null hypotheses (no difference), an adjustment allowing for treatment effects, when examined, would increase the validity of the ADI-R-JV.

In the present study, clinically referred and control individuals were enrolled according to different protocols. If caregiver motivation to participate in this study differed

for the two groups of individuals examined, the difference may have been a substantial source of sample bias. The most likely scenario related to this issue would be that a caregiver of a control individual was highly motivated to participate in the study when there was a concern that the child may have had an undiagnosed psychiatric disorder such as ASD. Indeed, such motivation might have been reflected in high proportions of non-ASD psychiatric disorders; 2 out of 16 control individuals in the reliability study (Table 1) and 4 out of 82 control individuals had such a diagnosis. Parental education and socioeconomic status, when available, may have provided some insight into the extent of this problem, but unfortunately we did not collect such data, which might otherwise have helped to refute this scenario. However, if such a motivation to participate in the study had indeed been the case, it is likely that a number of individuals with ASD would have been detected among control individuals, yet there was not a single case of undiagnosed ASD (i.e., later detected as such) among individuals initially enrolled as controls (Table 1 and Appendix Table 2 in supplementary materials). To minimize this ambiguity, confirmatory studies will be necessary.

Consensus clinical diagnoses were obtained through clinical assessments and case reviews of all of the available information, albeit outside the context of the administration of ADI-R-JV. This approach might have led to a lack of information for optimizing the diagnosis, but it ensured the independence of the administration of the ADI-R-JV. Moreover, ADI-R-JV was administered in a blinded fashion without any reference to the clinical consensus diagnosis, which could also be considered as a strength of the present study.

When we finalized our consensus clinical diagnosis, it might have been helpful to facilitate diagnosis derived from ADOS. It may also have been helpful to adopt this protocol as an external criterion for estimating the validity of ADI-R-JV. Indeed, the Japanese translation of ADOS has been available to those who established the research reliability of ADOS (i.e., since 2010). Our research team consists of very experienced clinicians and clinical researchers, and among the 8 team members involved in establishing a consensus clinical diagnosis, 4 had already established, and 2 were planning to establish, the research reliability of the ADI-R; 3 had already established, and 3 were planning to establish, the research reliability of ADOS; and each member had participated in at least one research training session on either ADI-R or ADOS. Thus, all the team members involved in establishing a consensus clinical diagnosis were fully knowledgeable about the current diagnosis of ASD in a research setting.

Conclusions

ADI-R-JV is a reliable tool, and has sufficient ability to discriminate between individuals with AD and other diagnoses, as well as between individuals with AD and those with no psychiatric diagnosis. The sensitivity for correctly diagnosing AD was generally high (92 %), but appeared to be compromised (55 %) when the tool was used to assess children younger than 5 years of age. The specificity of ADI-R-JV was consistently high, regardless of the age and cognitive level of the examinee.

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ORIGINAL PAPER

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

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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 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.

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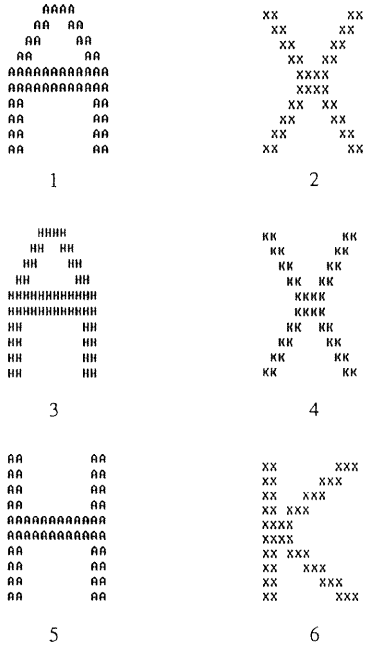

Fig. 1 Stimuli used in the divided-attention task (Plaisted et al. 1999)

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

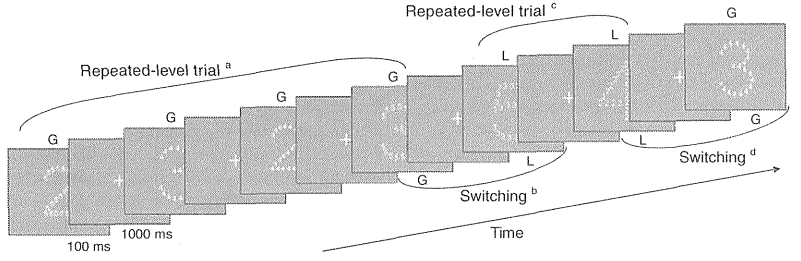

Fig. 2 Sequence of the experimental trials. The first repeated-level trial shows a switch after a four repeated-level trial, and the second shows a switch after a two repeated-level trial. *G* global-level target; *L* local-level target. *a* Four repeated-level trial (repetition of four global targets). *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	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

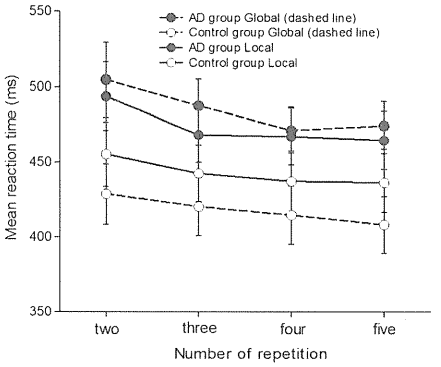

Fig. 3 Mean reaction times for repeated-level trials. *Bars* indicate the standard error of the mean. *AD* Asperger's disorder

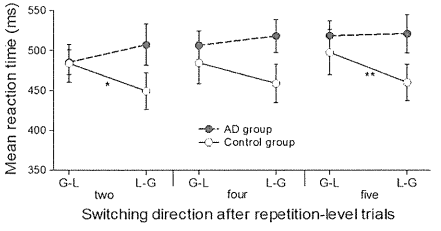

Fig. 4 Mean reaction times for switching trials. *G-L* indicates global-to-local switching after repeated-level trials, and *L-G* indicates local-to-global switching. *Two*, *four* and *five* indicate the number of repetitions in repeated-level trials. *Bars* indicate the standard error of the mean. *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

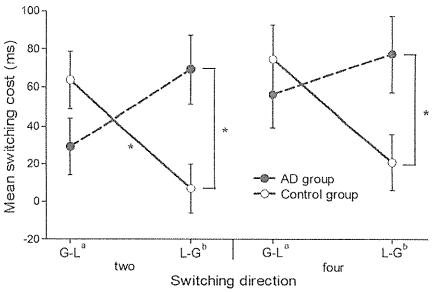

Fig. 5 Switching cost for switching trials. *G-L* indicates global-to-local switching after repeated-level trials, and *L-G* indicates local-to-global switching. *Two* and *four* indicate the number of repetitions in repeated-level trials. *Bars* indicate the standard error of the mean. *AD* Asperger's 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.

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TRIALS

STUDY PROTOCOL Open Access

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

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Abstract

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

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

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

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

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

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Background

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

Cognitive-behavioral therapy (CBT) interventions are being implemented within small group or individual therapy, with the aim of improving the regulation of emotions associated with ASD difficulties [11-15]. Sofronoff and colleagues [12] examined 71 children, aged 10 to 12 years, diagnosed with Asperger's syndrome (AS). In some cases, the children's parents were randomly assigned to one of three conditions (child-only intervention, child and parent intervention, and waitlist control). Small-group CBT was carried out, and the results for the three groups were compared among the three groups. Each of the intervention groups contained three participants, matched on sex and age. Two graduate student therapists conducted CBT for each group. There were 23 participants, over eight groups, in the child-only intervention group. Although there was no direct parental involvement, activities were explained after the sessions, and parents were instructed to have their children perform tasks at home. There were 25 participants, over nine groups, in the child and parent intervention condition. The interventions for the children in this condition were the same as those in the child-only intervention condition, with one psychotherapist for each group, which also included two parents. Twenty-three individuals were assigned to the control group. Six 2 hour sessions, during which participants studied how to be emotionally aware and use appropriate methods for coping with emotions, were conducted over 1 week. Results were examined via children's self-assessments using the "James and the Maths Test", a story describing anxiety about a math test. The parents also completed an assessment using the Spence Child Anxiety Scale and Social Worries Questionnaire–Parent. These assessments were performed at pre- and post-intervention, and also during a follow-up session (6 weeks later). A significant intervention effect was observed when both children and parents took part in the intervention; the child-only intervention was the next most effective treatment. Furthermore, a randomized comparative trial conducted by Sofronoff and colleagues [13] revealed similar results for a small-group CBT intervention to help with anger control. Based on the efficacy of the emotion-regulation which these studies showed, the Cognitive Affective Training Kit (The Cat-kit) was developed [16]. It is designed to help individuals with ASD become aware of how their thoughts, feelings and actions all interact and, in the process of using the various visual components, they share their insights with others.

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

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

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

Objectives

The purpose of this study is to investigate the efficacy of group-based CBT for adults with ASD. Our primary hypothesis is that, through group-based CBT focusing on emotion-regulation and psychoeducation about ASD, adults with ASD can understand their own and others' emotions and thoughts, exercise emotion-regulation, and increase their knowledge of ASD and self-awareness, especially of their own strengths and weaknesses related to ASD. A small-group adult CBT study protocol will be prepared with reference to previous CBT studies. As noted above, parent training, as well as other forms of intervention, can be carried out along with a child's CBT. Thus, parents gain a greater understanding of ASD and the necessary modifications to a child's environment, which is highly effective in enabling a parent being able to adapt to a child with ASD. However, unlike in children, adults with ASD need to understand more about their own strengths and weaknesses, as it is more desirable and practical that they are able to modify their own environment instead of his/her parents. Therefore, this study, which attempts to help improve social adaptation among adults with ASD, comprises two programs: (1) increasing the individual's emotional awareness and allowing them to acquire appropriate coping skills, and (2) increasing self-awareness through ASD psychoeducation, by learning about the symptoms and biological cause of ASD and the individual's strengths and weakness associated with it. These programs will be provided regularly, and the effects of these programs will be assessed.

Methods/Design

Trial design

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

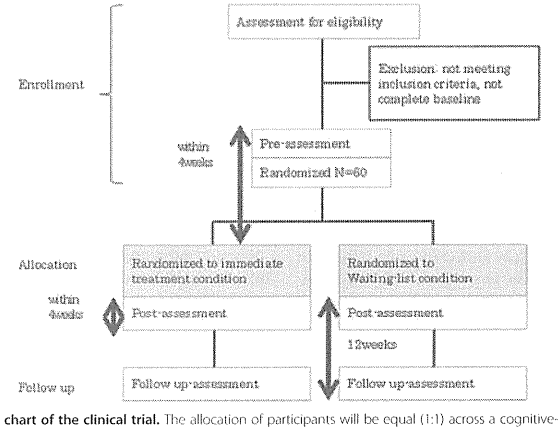

Figure 1 CONSORT flow chart of the clinical trial. The allocation of participants will be equal (1:1) across a cognitive-behavioral therapy group and a waitlist control group. All assessment will be administrated at the enrolment, post-intervention, and at 12 weeks follow-up. Both pre- and post-assessment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

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

The target sample size is 60, and registration began on September 1, 2011. This trial was registered in the University Hospital Medical Information Network Clinical Trials Registry and approved by the International Committee of Medical Journal Editors (No. UMIN000006236).

Ethical consideration

The Ethics Committee of the National Institute of Neurology and Psychiatry (No. A2010-022) and Graduate School of Medicine and Faculty of Medicine at the University of Tokyo have approved the study protocol (No. 2702). All participants will be asked to sign a written informed consent, as approved by the ethical committee of each site, according to the Declaration of Helsinki after receiving a complete explanation of the trial.

Participants

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

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

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

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

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

Inclusion criteria

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

Exclusion criteria

- A psychiatric comorbid and/or unstable condition

As shown in Table 1, candidates will be provided with a detailed diagnostic confirmation using the Autism-Spectrum Quotient, Japanese version [23], which is a self-report questionnaire measuring the degree to which any adult with a normal IQ possesses traits related to the autistic spectrum. Additional measures will include the Social Responsiveness Scale for Adults, Japanese version [24], which measures the severity of autism spectrum symptoms (completed by a relative), and the Empathizing- Systemizing Quotient, Japanese version [25], which assesses a person's strength of interest in empathy (defined as the drive to identify with a person's thoughts and feelings and respond with an appropriate emotion). A person's strength of interest in systems is defined as the drive to analyze or construct a system. Additionally, interviews using the ADOS for individuals with ASD and interviews with parents using the ADI-R will be conducted. Final participation will be decided after confirmation that the subject meets participation criteria.

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

Assessments/measures

Primary outcomes

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

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

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

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

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

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

Secondary outcomes

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

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

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

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

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

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

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

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

Details of the intervention program

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

Table 2 Timetable of one session

Schedule		
5 minutes	Greeting	
30 minutes	Psychoeducation on autism spectrum disorders	
10 minutes	Relaxation	
40 minutes	Work and discussion	
	<Topics>	
	Session 1 Autism spectrum disorders	Session 2 Relaxation
	Session 3 Happiness	Session 4 Comfort
	Session 5 Affection	Session 6 Anxiety
	Session 7 Anger	Session 8 Coping skills
5 minutes	Relaxation	

period of relaxation between topics (Table 2). Group therapy consists of four to five adults with ASD and two therapists. The therapist who conducts the group therapy as the leader is the certified developmental psychologist who has a PhD and over 10 years experience working with individuals with ASD. The other therapist, the sub-leader, is also a psychologist and has a Masters degree. One or two typical-development volunteers will also join the group and do the same program as the participants with ASD.

The program has two parts; one is the psychoeducation on ASD and the other is the emotion-regulation program. Materials for the psychoeducation on ASD prepared for this study will be used for learning and understanding the nature of ASD. The Cat-kit [16] will be used for the emotion-regulation program. The titles of each session are as follows: (1) the characteristics of autism; (2) relaxation 1 and happiness; (3) relaxation 2 and comfort; (4) differences from others and sadness; (5) strengths and anxiety; (6) weaknesses and coping with anxiety; (7) anger and coping methods; (8) summary: autism characteristics and conveying emotions.

During each session, participants will be asked to do some written work. For the part of psychoeducation on ASD, they will describe and present their own preferences, strengths, weaknesses, *et cetera*. In the emotion-regulation program, they will present their experience and physiological changes associated with emotion. The typical-development volunteers will also perform the same tasks. Finally, after completion of the intervention, the individuals with ASD will make out an original notebook containing descriptions of the nature of ASD and emotion-regulation learning and they will be encouraged to use this for continued study.

Randomization

Enrollment and random allocation will be performed through central registration at the University Hospital Clinical Trial Alliance Clinical Research Supporting System (UHCT ACReSS) at the University of Tokyo. A minimization method will be used with sex as the allocation factor. A third party, who is not involved in this trial, will enroll participants after examining their eligibility and informed consent. Owing to allocation concealment, the random allocation sequence will be provided by UHCT ACReSS and will not be revealed to any researchers or staff until the end of the enrollment period. As this is a single-blinded trial, all assessments will be conducted by raters without knowledge of whether the participant is in the CBT or waitlist conditions.

Statistical methods

All analyses will be performed using SPSS 20 J (SPSS Inc., Chicago, IL, USA). All data will be analyzed under the intent-to-treat principle. For the primary outcomes, independent *t*-tests will be used to compare changes in scores between the pre-assessment and post-assessment periods between the CBT group and the waitlist control group. The primary outcomes will be analyzed controlling for potential confounds (for example, age, gender, IQ, and clinical characteristics) using regression models. Secondary outcomes will be analyzed using relevant tests at each assessment, controlling for possible confounds as described above. Subgroup analyses will be performed for any possible confounds to differentiate the efficacy of CBT at follow-up.

Discussion

Expected results are that adults with ASD will be able to identify their own and understand others' mental states. We further predict that our CBT group will improve their coping skills. Furthermore, secondary symptoms, such as anxiety or depression, should reduce and adaptive behaviors should improve. The novelty of this trial lies in the utilization of CBT for improving emotion regulation among adults with ASD, in contrast with previous studies, which have included children and adolescents (up to age 16) as participants. Previous studies have also focused on the management of anxiety or anger whereas one of our study objectives is to manage the self-regulation of emotion in general. Moreover, previous studies have implemented CBT for children with ASD in addition to parental training. The current study will focus on psychoeducation regarding ASD for adult patients; that is, the current study does not include parent training as a means of the subject's understanding ASD. Thus, our design should help to determine the efficacy of CBT for adults with ASD. This CBT intervention is the first step in understanding ASD and emotion-regulation in adulthood, especially for persons diagnosed with ASD in adulthood. Our results will hopefully provide promising avenues for developing services for adults with high-functioning ASD in Japan.

Trial status

At the time of submission, 88% of the participants have been included in the trial. Of these participants, 68% have been tested at follow-up.

Abbreviations

ADOS: Autism Diagnostic Schedule; ADI-R: Autism Diagnostic Interview, Revised; AS: Asperger's syndrome; ASD: autism spectrum disorders; Cat-kit: Cognitive Affective Training Kit; CBT: cognitive-behavioral therapy; CES-D: Center for Epidemiological Studies Depression Scale; CISS: Coping Inventory for Stressful Situations; DSM-IV-TR: text revision of the diagnostic and statistical manual of mental disorders, fourth edition; GAF: Global Assessment of Functioning; IQ: intelligence quotient; LSAS: Liebowitz Social Anxiety Scale; MPMR: Motion Picture Mind-Reading task; STAI: State-trait Anxiety Inventory; SPAI: Social Phobia and Anxiety Inventory; TAS-20: 20-item Toronto Alexithymia Scale; UHCT ACReSS: University Hospital Clinical Trial Alliance Clinical Research Supporting System; WHO-QOL 26: World Health Organization Quality of Life 26-item version.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MK and YK equally contributed to the design and management of this trial and wrote most of the manuscript. HK made substantial contributions to the conception and design of this trial. KY contributed to the development of the CISS-Japanese version. YK and YK are the directors of each site and made substantial contributions to revising the design and management of this trial. All authors have read and approved the final manuscript.

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Altered automatic face processing in individuals with high-functioning autism spectrum disorders: Evidence from visual evoked potentials

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ABSTRACT

Individuals with autism spectrum disorders (ASDs) have different automatic responses to faces than typically developing (TD) individuals. We recorded visual evoked potentials (VEPs) in 10 individuals with high-functioning ASD (HFASD) and 10 TD individuals. Visual stimuli consisted of upright and inverted faces (fearful and neutral) and objects presented subliminally in a backward-masking paradigm. In all participants, the occipital N1 (about 100 ms) and P1 (about 120 ms) peaks were major components of the evoked response. We calculated "subliminal face effect (SFE)" scores by subtracting the N1/P1 amplitudes and latencies of the object stimuli from those of the face stimuli. In the TD group, the SFE score for the N1 amplitude was significantly higher for upright fearful faces but not neutral faces, and this score was insignificant when the stimuli were inverted. In contrast, the N1 amplitude of the HFASD subjects did not show this SFE in the upright orientation. There were no significant group differences in SFE scores for P1 amplitude, latency, or N1 latency. Our findings suggest that individuals with HFASD have altered automatic visual processing for emotional faces within the lower level of the visual cortex. This impairment could be a neural component of the disrupted social cognition observed in individuals with HFASD.

Social dysfunction is a fundamental problem in autism spectrum disorders (ASDs). Consequently, face processing in individuals with ASD has been intensively studied on both the behavioral and neurological level. A range of face processing abnormalities has been described in individuals with ASD (Behrmann et al., 2006; Berger, 2006; Dawson, Webb, & McPartland, 2005; Grelotti, Gauthier, & Schultz, 2002; Sasson, 2006; Schultz, 2005), and their relatives (Baron-Cohen & Hammer, 1997; Bölte & Poustka, 2003; Wallace, Sebastian, Pellicano, Parr, & Bailey, 2010). Some researchers have proposed face processing as a candidate for a cognitive ASD endophenotype (Dawson et al., 2002; Wallace et al., 2010; Wilson, Brock, & Palermo, 2010).

Face processing relies on a distributed, patchy network of cortical regions and subcortical structures (Atkinson & Adolphs, 2011). The core cortical regions include the inferior occipital gyri (early perception of facial features), the lateral fusiform

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gyrus (perception of unique identity) and the superior temporal sulcus (perception of eye gaze, expression, and lip movement; Calder & Young, 2005). The non-conscious perception of emotional stimuli appears to involve several subcortical structures, which comprise two subsystems (Tamietto & de Gelder, 2010). One is the visually related emotion-encoding subsystem, which includes the amygdala, and the other is the non-visual emotion-encoding subsystem. These subcortical structures modulate cortical face processing (Tamietto & de Gelder, 2010). Further, these subcortical structures have been reported to be sensitive to low spatial frequency (SF) information about the emotional content of faces (Nakashima et al., 2008; Vlamings, Goffaux, & Kemner, 2009; Vuilleumier, Armony, Driver, & Dolan, 2003).

Emotionally significant stimuli, such as threat-related or social information, are first automatically processed outside of conscious awareness before being integrated with slower and more elaborative processing (Johnson, 2005). Abnormalities in automatic emotional processing are thought to be a key source of disrupted social cognition in individuals with ASD (Bailey, Braeutigam, Jousmäki, & Swithenby, 2005; Critchley et al., 2000). In accordance with this concept, our earlier behavioral study found that individuals with ASD responded to emotional faces differently than typically developing (TD) individuals, at an automatic level (Kamio, Wolf, & Fein, 2006). In contrast, ASD participants had normal performance for face tasks at a conscious level (Kamio et al., 2006a). Despite these findings, the neural basis of abnormal automatic processing of emotional faces in individuals with ASD remains uncertain.

The measurement of visual evoked potentials (VEPs) is an objective tool that has been useful in studies investigating the physiology and pathophysiology of the human visual system, including visual pathways and the visual cortex (Tobimatsu & Celesia, 2006). In particular, VEPs have high temporal resolution and are therefore suitable for the investigation of early automatic face processing. The major components evoked by conscious face stimuli are the occipital N1 (around 100 ms) and P1 (around 120 ms) peaks, and the occipito-temporal N170 (around 170 ms) peak (Bötzel, Schulze, & Stodieck, 1995; George, Evans, Fiori, Davido, & Renault, 1996). Both the N1 and P1 reflect the coarse processing of faces within the primary visual cortex (V1; Goto, Kinoe, Nakashima, & Tobimatsu, 2005; Mitsudo, Kamio, Goto, Nakashima, & Tobimatsu, 2011; Nakashima et al., 2008), whereas the N170 plays a role in processing features of faces or facial identification within the fusiform face area (FFA; Bentin, Allison, Puce, Perez, & McCarthy, 1996). When a supra-threshold face is inverted (the so-called "face inversion effect"), the N170 shows increased amplitude and delayed latency (Jacques, d'Arripe, & Rossion, 2007). This effect results from impaired integration of the features into a gestalt or holistic face representation (Young, Hellawell, & Hay, 1987). We recently reported that in healthy participants, occipital P1 amplitudes for unrecognizable (subliminal) faces are significantly larger than those for objects in the upright position (Mitsudo et al., 2011). However, P1 amplitudes for inverted faces are significantly smaller than those for upright faces. This is opposite to the face inversion effect for supra-threshold stimuli. Here, we call this phenomenon the "subliminal face effect (SFE)". Therefore, we consider that faces and objects are processed differently at the V1 level, even when the subjects are unaware of the stimuli before the face-specific processing occurs within the FFA. Taken together, changes in N1 or P1 in response to subliminal upright and inverted faces could provide an insight into the neural basis of automatic face processing in high-functioning ASD (HFASD).

In the present study, we hypothesized that individuals with HFASD have abnormal automatic processing at the V1 level (SFE in the upright or inverted orientation). To test this hypothesis, we used a 128-channel EEG system to record VEPs elicited by subliminally presented faces (fearful and neutral) and objects in the upright and inverted position. We measured the amplitudes and latencies of N1 and P1 peaks in response to these visual stimuli in HFASD and TD adults and calculated the SFE to quantify automatic face processing. We predicted that individuals with HFASD would exhibit a different pattern of V1 responses to masked subliminal faces in different orientations than TD individuals.

1. Methods

1.1. Participants

Ten individuals with HFASD (7 males and 3 females, aged 23–39 years, mean age 31.5) and 10 healthy TD control individuals (8 males and 2 females, aged 19–39 years, mean age 26.8) participated in this study. HFASD participants included four individuals with Asperger syndrome, one individual with high-functioning autism, and five individuals with pervasive developmental disorder not otherwise specified. The HFASD participants were recruited from the local Autism Society and local specialized psychiatric clinic. Diagnoses of ASD were confirmed, according to the DSM-IV-TR criteria (American Psychiatric Association, 2000), by a clinical research team that included an experienced child psychiatrist (Y.K.). ASD diagnoses were corroborated by a parental semi-structured interview that was developed and validated for Japanese populations with ASD, with a sensitivity of 0.943–0.975 and specificity of 0.929–0.956 (the PDD-Autism Society Japan Rating Scale [PARS]; Ito et al., 2012; Kamio et al., 2006b). Diagnostic agreement among the team was obtained for all participants. Although two of the 10 HFASD participants were being treated with small doses of antidepressants (1 with serotonin and noradrenalin reuptake inhibitors, 1 with quadricyclic antidepressants and selective serotonin reuptake inhibitors) at the time of participation, their symptoms were in remission and these individuals were psychologically stable. We evaluated intellectual function of the HFASD participants using the Japanese version of the Wechsler Adult Intelligence Scale-Revised. Individuals with ASD who had a full-scale IQ score lower than 85 were not included in the study.

TD control subjects were local college students and members of our faculty, who were interviewed to confirm the absence of any developmental or neuropsychiatric history, and/or medical conditions. None of the control participants were currently taking medication. TD control participants were confirmed to have normal intellectual functioning via interviews,

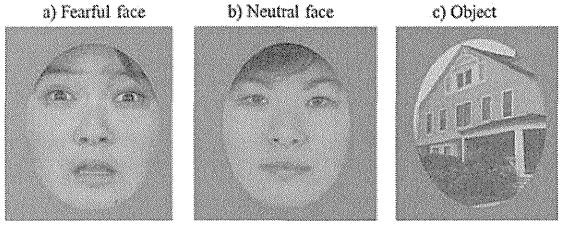

Fig. 1. Representative examples of fearful face (a), neutral face (b) and object (c) stimuli used in this study. Face stimuli are taken from the standardized Japanese and Caucasian Facial Expressions of Emotion and the Japanese and Caucasian Neutral Faces photo sets by Matsumoto and Ekman (1988). All stimuli are grayscale photographs (visual angle, 10°; mean luminance, 6 cd/m^2). The pattern mask is a 1024 × 768 pixel noise pattern.

although we did not conduct cognitive testing. All participants exhibited normal or corrected-to-normal visual acuity (>1.0), evaluated using the Landolt ring (Landolt, 1905).

1.2. Visual stimuli

The stimuli were generated by ViSaGe (Cambridge Research Systems, Cambridge, U.K.) and displayed on a gamma-corrected color monitor with a frame rate of 100 Hz (Electron22blue IV, LaCie, Tokyo, Japan). Photographs of eight fearful and eight neutral faces from 16 individuals (8 men and 8 women) were taken from Matsumoto and Ekman's (1988) standardized set of Japanese and Caucasian Facial Expressions of Emotion, and Japanese and Caucasian Neutral Faces (Fig. 1a and b). Half of the photographs were of people of Asian descent and the other half were of people of Caucasian descent. All photos were of faces viewed from the front with no hair visible. Eight different objects (e.g., house, chair) were selected as the object stimuli (Fig. 1c). Eight cartoon characters were used as the target stimuli. All pictures were grayscale photographs (visual angle, 10°; mean luminance, 6 cd/m^2). We used a 1024 × 768 pixel noise pattern generated by Adobe Photoshop 7.0 as a pattern mask.

1.3. Threshold setting

We conducted a pilot experiment to identify the sub-threshold duration at which participants would be able to determine whether the masked stimuli were faces or objects. This was done using a separate group of participants (3 HFASD and 6 TD) recruited from our volunteer pool. In this experiment, we used an ascending series of trials to prevent participants from perceiving the contents of the stimuli, as in previous studies (Mitsudo et al., 2011; Wolf, Kamio, & Fein, 2001). In each trial, masked stimuli (neutral and fearful faces, objects) were randomly presented, and participants verbally reported what they saw. In the first trial block, the stimulus presentation was 10 ms long. This duration increased in each subsequent trial block in 10 ms steps. Stimuli were presented 20–30 times in each trial block. The threshold at which participants first reported that they saw a human-like silhouette ranged between 30 and 80 ms, with a mean of 56.7 ms for the TD individuals and 56.7 ms for the HFASD individuals. Based on the results of this experiment, we set the duration of sub-threshold presentation in the current study at 20 ms.

1.4. VEP recordings

The VEP experiment was conducted in a dimly lit and electrically shielded room. Participants sat in front of the monitor at a viewing distance of 114 cm. VEPs were recorded using a Geodesic EEG system, NetAmps 200 (Electrical Geodesics [EGI], Eugene, OR). A high-density, 128-channel, HydroCel Geodesic Sensor net (EGI) was applied over the scalp of each participant. This net held each electrode in place, and distributed electrodes from the nasion to the inion and from the left to the right mastoid processes at uniform intervals. Each electrode consisted of a silver chloride carbon fiber pellet, a lead wire, a gold-plated pin, and a potassium chloride-soaked sponge. This electrode configuration effectively blocked out electrochemical noise and minimized triboelectric noise. Signals were amplified via an AC-coupled, 128-channel, high-input impedance amplifier (NetAmps 200, EGI). The analog data were digitized at a sampling rate of 500 Hz/channel. Amplified analog voltages were hardware band-pass-filtered at 0.1–200 Hz. The experimenter individually adjusted all sensors until the impedance of each electrode was less than 50 kΩ (Ferree, Luu, Russell, & Tucker, 2001). We used the vertex (Cz) electrode as a reference.

1.5. VEP tasks

Face (fearful, neutral) and object stimuli were randomly presented in six blocks composed of 150 trials with six different stimulus categories: upright fearful faces (150), inverted fearful faces (150), upright neutral faces (150), inverted neutral

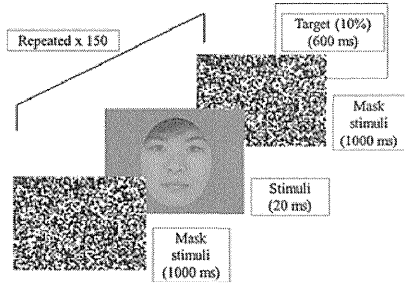

Fig. 2. Experimental procedures. The faces and objects were randomly presented for 20 ms (sub-threshold duration) in the upright or inverted orientations, followed by a 1000 ms pattern mask. The target appears in 10% of the trials in each block and is presented for 600 ms to draw the participant's attention away from the experimental stimuli.

faces (150), upright objects (150), inverted objects (150). These stimuli were presented for 20 ms followed by a pattern mask for 1000 ms. During debriefing, we confirmed that all participants were unable to recognize either the face or object stimuli. The target, which appeared in 10% of the total trials in each block, was intermixed and randomly presented for 600 ms to shift the participant's attention away from the face and object stimuli. Participants were asked to respond by pressing a button as accurately and quickly as possible when they saw the target stimulus appear on the screen (Fig. 2).

Participants were instructed to remain still and to fix their gaze on a black dot at the center of the screen. Arousal level was carefully visually monitored by an observer (T.F.) in the same room and by the EEG signal. We also recorded each participant's activity using a video camera placed outside of the room. If a participant became drowsy, he/she was alerted and provided with a brief rest period.

Informed consent was obtained from all participants and from the parents of minor participants. The experimental procedures were approved by the ethics committee of the Graduate School of Medical Sciences, Kyushu University.

1.6. Data analysis

1.6.1. Behavioral performance

In order to confirm that participants were attending to the target stimuli, we measured the mean reaction time and correct detection rate. The group differences on these measures were evaluated using a two-way analysis of variance (ANOVA) with repeated measures (stimulus orientation × participant group).

1.6.2. VEP data

For the VEP analysis, stimulus epochs began 50 ms prior to stimulus onset and continued for 500 ms after. Epochs containing EEG deviations 50 μV greater than baseline were automatically rejected. Epochs containing blinks, horizontal or non-blink eye movements, analog to digital conversion (A/D) saturation, or obvious occipital α-activity were rejected. The electrodes surrounding the eyes were used to identify blinks and horizontal or non-blink eye movements. They were then re-referenced offline to an average of 99 channels, which represented all channels except for the channels around the eyes, ears, and neck because these channels were easily contaminated by the electric potential of muscles. Finally, in the accepted samples, 550 ms epochs were averaged in each stimulus category using Net Station software (EGI). The number of accepted samples per stimulus category across the participants was at least 120 (80%).

The major VEP components obtained for all participants in both groups were the N1 and P1 peaks, which were recorded over occipital regions (maximum at the Oz electrode). The P300 (maximum at the Pz electrode) was also evoked by the target stimulus in all participants except one HFASD female participant, who did not show the P300 component and was thus excluded from subsequent statistical analyses. Our small sample size increased the possibility of type II error. To address this, we used a two-way ANOVA with repeated measures (stimulus orientation × participant group) to examine group differences in the amplitude and latency of P300 for the target stimuli at the Pz electrode. A three-way ANOVA with repeated measures was also performed to examine the effects of stimulus type, stimulus orientation, and participant group on the amplitudes and peak latencies of the N1 and P1 components at the Oz electrode. Since our research concerns the relative impact of subliminal faces over objects on N1 and P1, SFE scores were further calculated by subtracting the N1/P1 amplitudes or latencies at the Oz electrode for object stimuli (baseline) from those for fearful or neutral face stimuli. This was done for each stimulus orientation, by group. These effects were analyzed using a three-way ANOVA with repeated measures (stimulus type × stimulus orientation × participant group). Bonferroni's correction was used for multiple comparisons. In all statistical analyses, a level of $p < 0.05$ was accepted as statistically significant.

2. Results

2.1. Intellectual function and behavioral performance in target detection

One of the ten participants in the HFASD group was excluded from further analyses because of a complete absence of P300 (see Section 1.6.2). The remaining nine participants (7 males and 2 females, aged 23–39 years, mean age 30.9) exhibited normal IQs (verbal IQ, 105.6 ± 19.1 [mean ± *SD*]; performance IQ, 104.7 ± 14.0; full-scale IQ, 105.7 ± 13.2). There were no significant effects of chronological age (*t* test: $t = -1.266$, $p = 0.22$) or sex (χ^2 test: $\chi^2 = 0.01$, $p = 1.00$) between the two groups. Neither the effect of any variable nor the two-way interaction between stimulus orientation and participant group were significant in terms of mean reaction time or correct detection rates (Tables 1 and 2). These results confirm that the participants in both groups were attentive to nearly the same degree during the experiment.

2.2. VEP responses

2.2.1. P300, N1, and P1 distribution for the TD and HFASD groups

The P300 component (maximum at Pz) was evoked when both groups viewed the target stimuli in the upright and inverted orientations. In terms of P300 amplitude and latency, there were no significant effects or interactions between stimulus orientation and participant group (Tables 1 and 2).

Grand-averaged VEP waveforms at the Oz electrode elicited by each stimulus in the upright and inverted orientations are shown in Fig. 3. In both groups, N1 (around 100 ms) and P1 (around 120 ms) were major components of the elicited waveform. Fig. 4 shows the scalp topography of N1.

2.2.2. Behaviors of N1 and P1 components

As shown in Figs. 3 and 4, the N1 and P1 components were modulated by participant group and stimulus type. The mean peak amplitudes and latencies of N1 and P1 for each stimulus are summarized for each group in Table 3. Table 4 summarizes the results of the ANOVA analysis. The N1 latency and the P1 latency and amplitude were unaffected by the stimulus conditions. However, the N1 amplitudes were modulated: there was a significant interaction effect between stimulus type, stimulus orientation, and participant group ($F(2, 34) = 7.12$, $p < 0.005$). In the TD group, we found a significantly larger N1 amplitude for fearful faces in the upright orientation compared with that for objects in the upright orientation ($p < 0.05$). This was not the case when the faces and objects were inverted. In the HFASD group, there were no significant differences in N1 amplitude among the stimuli in both the upright and inverted orientations.

2.2.3. SFE scores for upright and inverted faces

We calculated the SFE scores for the N1 and P1 peaks for each stimulus and each group (Table 5 and Fig. 5). The results of the ANOVA are summarized in Table 6. A significant 3-way interaction between stimulus type, stimulus orientation, and participant group was found for N1 amplitude only ($F(1, 17) = 9.23$, $p < 0.01$). Multiple comparisons revealed that the SFE score for upright fearful faces in the TD group was significantly greater than that for inverted fearful faces ($p < 0.05$). This finding indicates that faces, specifically fearful but not neutral faces ("emotion effect"), elicited a significantly greater N1 amplitude than objects in the TD group. The SFE was absent when the stimuli were inverted (Table 5 and Fig. 5). In contrast,

Table 1
Performance and P300 in response to the target stimuli in the TD and HFASD groups.

Groups	Stimulus orientation	Performance		P300	
		Reaction time (ms)	Correct detection rate (%)	Amplitude (μV)	Latency (ms)
TD group ($n = 10$)	Upright	446.4 ± 33.4	93.2 ± 5.5	5.5 ± 2.2	341.0 ± 61.2
	Inverted	448.9 ± 53.4	91.3 ± 7.9	5.3 ± 2.2	335.4 ± 30.2
HFASD group ($n = 9$)	Upright	443.0 ± 48.4	88.3 ± 10.2	5.0 ± 5.1	339.6 ± 53.7
	Inverted	442.8 ± 55.7	85.1 ± 9.8	4.7 ± 4.5	370.0 ± 73.8

Data are expressed as mean ± *SD*.

Table 2
Results of two-way ANOVA in performance and P300 in response to the target stimuli.

Factors	Performance				P300			
	Reaction time		Correct detection rate		Amplitude		Latency	
	F-value	*p*-Value	*F*-value	*p*-Value	*F*-value	*p*-Value	*F*-value	*p*-Value
Orient	0.05	0.82	1.60	0.22	0.00	1.00	0.85	0.37
Partic	0.01	0.91	4.38	0.052	0.00	1.00	0.55	0.47
Orient × Partic	0.01	0.93	0.06	0.81	0.00	1.00	1.80	0.20

Abbreviations in this and subsequent tables: Orient, stimulus orientation (upright, inverted); Partic, participant groups (HFASD, TD).

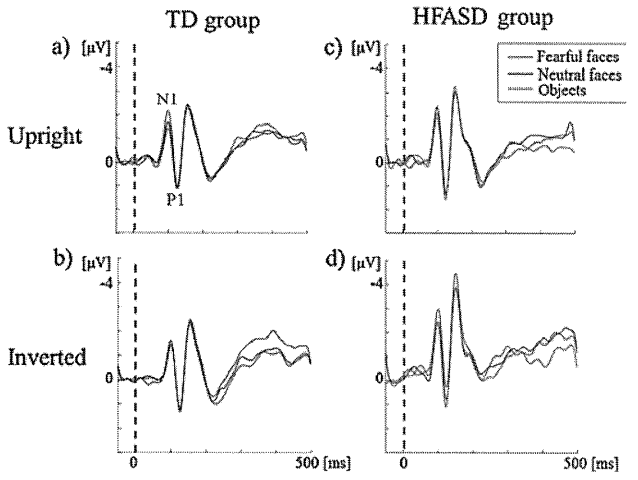

Fig. 3. Grand-averaged VEP waveforms at the Oz electrode in response to each stimulus in the TD ($n = 10$) (a, b) and HFASD ($n = 9$) (c, d) groups. In both groups, the stimulus (in both orientations) elicited the negative component at approximately 100 ms (N1) and the following positive peak at about 120 ms (P1) after stimulus onset.

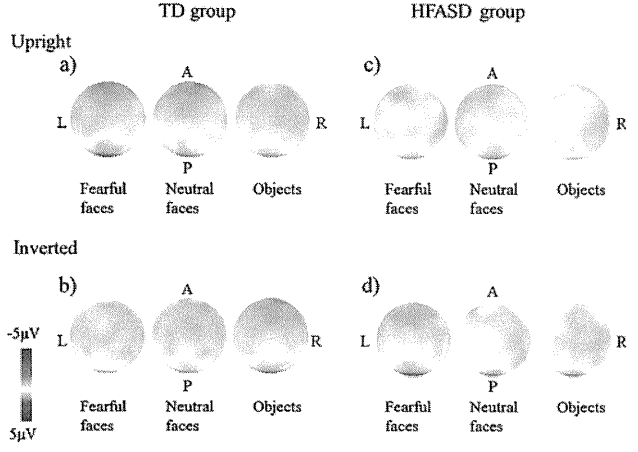

Fig. 4. Grand-averaged scalp topography of the N1 component in the TD ($n = 10$) (at 100 ms) (a, b) and HFASD ($n = 9$) groups (at 100 ms) (c, d). The N1 components were predominant over the occipital regions (maximal at the Oz electrode) when participants in both groups viewed stimuli in both the upright (a, c) and inverted (b, d) orientations. There are substantial differences in the scalp topography between the two groups depending on stimulus type and orientation. L: left, R: right, A: anterior, P: posterior.

the SFE score of the N1 amplitude in the HFASD group did not differ between upright or inverted fearful and neutral faces, indicating the absence of SFE for upright and inverted faces in this group. Between the two groups, the SFE score of the N1 amplitude for fearful faces was significantly larger in the TD group compared with that of the HFASD group in the upright condition ($p < 0.05$) but not the inverted condition (Table 5 and Fig. 5).

Table 3
Peak amplitudes and latencies of N1 and P1 (mean ± *SD*) at the Oz electrode in the TD and HFASD groups.

Stimulus		N1		P1	
		Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)
(a) TD group (n = 10)					
Upright	Fearful	2.5 ± 0.7*	99.6 ± 6.3	1.6 ± 2.3	127.0 ± 5.2
	Neutral	2.1 ± 0.9	99.2 ± 7.7	1.7 ± 1.8	127.4 ± 5.9
	Object	1.8 ± 0.7	98.6 ± 9.3	1.7 ± 1.8	126.6 ± 6.4
Inverted	Fearful	2.0 ± 0.7	99.4 ± 9.3	1.7 ± 1.7	127.2 ± 5.7
	Neutral	2.0 ± 1.0	99.4 ± 10.1	1.8 ± 1.7	126.8 ± 5.8
	Object	2.1 ± 0.9	99.8 ± 7.9	1.8 ± 1.8	125.6 ± 6.6
(b) HFASD group (n = 9)					
Upright	Fearful	2.0 ± 1.9	97.6 ± 6.8	1.6 ± 1.5	124.0 ± 3.7
	Neutral	2.3 ± 2.0	98.4 ± 5.1	1.6 ± 1.9	124.0 ± 4.1
	Object	2.2 ± 2.1	97.3 ± 5.7	1.9 ± 2.2	123.0 ± 4.1
Inverted	Fearful	2.9 ± 2.7	98.4 ± 6.2	0.5 ± 1.5	124.0 ± 3.5
	Neutral	2.4 ± 2.6	97.8 ± 6.1	0.9 ± 1.1	124.0 ± 2.8
	Object	2.3 ± 2.5	96.0 ± 5.1	1.3 ± 1.5	122.0 ± 3.5

* Upright fearful face vs. Upright object, $p < 0.05$.

Table 4
Results of three-way ANOVA in N1 and P1.

Factors	N1				P1			
	Amplitude		Latency		Amplitude		Latency	
	F-value	*p*-Value	*F*-value	*p*-Value	*F*-value	*p*-Value	*F*-value	*p*-Value
Stim	1.51	0.24	3.19	0.054	1.99	0.15	5.56	**<0.01**
Orient	0.44	0.52	0.00	0.98	1.54	0.23	3.94	0.06
Partic	0.51	0.48	0.28	0.60	0.31	0.59	2.03	0.17
Stim × Orient	0.56	0.58	0.18	0.84	0.27	0.77	2.06	0.14
Stim × Partic	0.11	0.90	1.87	0.17	1.09	0.35	0.09	0.91
Orient × Partic	1.62	0.22	0.60	0.45	2.66	0.12	0.20	0.66
Stim × Orient × Partic	7.12	**<0.005**	1.64	0.21	0.33	0.72	0.04	0.96

Abbreviations in this and subsequent tables: Stim, stimulus types (neutral faces, feareful faces, objects).
Bold values indicate significance.

Table 5
"Face effect" scores for N1 and P1 (mean ± *SD*) in the TD and HFASD groups.

Stimuli		N1		P1	
		Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)
(a) TD group (n = 10)					
Upright	Fearful faces minus Objects	0.8 ± 0.6*, #	1.0 ± 4.8	0.1 ± 1.0	0.4 ± 2.3
	Neutral faces minus Objects	0.3 ± 1.0	0.6 ± 3.1	0.0 ± 0.9	0.8 ± 2.1
Inverted	Fearful faces minus Objects	−0.1 ± 0.6	−0.4 ± 2.6	0.1 ± 0.8	1.6 ± 1.8
	Neutral faces minus Objects	−0.1 ± 0.6	−0.4 ± 3.1	0.0 ± 0.5	1.2 ± 2.1
(b) HFASD group (n = 9)					
Upright	Fearful faces minus Objects	−0.2 ± 1.0	0.2 ± 1.9	0.0 ± 1.0	1.1 ± 2.7
	Neutral faces minus Objects	0.1 ± 0.7	1.1 ± 1.5	−0.2 ± 1.1	1.1 ± 2.7
Inverted	Fearful faces minus Objects	0.6 ± 1.2	1.8 ± 3.5	0.7 ± 1.6	2.0 ± 2.0
	Neutral faces minus Objects	0.1 ± 0.5	2.0 ± 2.4	0.3 ± 1.1	1.8 ± 2.1

* Upright fearful faces minus Objects vs. Inverted fearful faces minus Objects, $p < 0.05$.
\# TD groups vs. HFASD group, $p < 0.05$.
See also Fig. 5.

P1 amplitude, P1 latency, and N1 latency revealed no significant SFE for either fearful or neutral faces in either stimulus orientation and in either group.

3. Discussion

In the present study, we measured VEPs in response to masked subliminal faces and objects to investigate the early stages of visual processing underlying automatic or implicit face processing in adults with HFASD. Our results show that the face stimuli evoked two major occipital components (N1 and P1) in adults with and without ASD, even though the masked faces

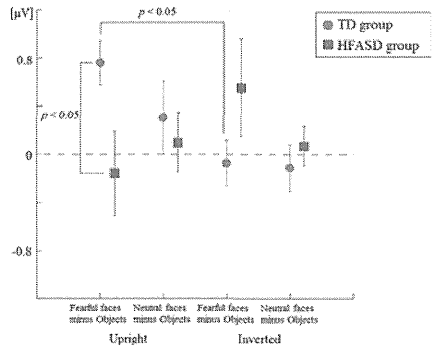

Fig. 5. Differences in N1 amplitude for faces relative to objects between the TD ($n = 10$) (red filled circle) and HFASD ($n = 9$) (blue filled square) groups. In the TD group, the N1 amplitude for fearful faces relative to objects in the upright orientation was significantly larger than that in the inverted orientation ($p < 0.05$) and that of the HFASD group in the upright orientation ($p < 0.05$). Results are shown ± SEM. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 6
Results of three-way ANOVA in "Face effect" score for N1 and P1.

Factors	N1				P1			
	Amplitude		Latency		Amplitude		Latency	
	F-value	*p*-Value	*F*-value	*p*-Value	*F*-value	*p*-Value	*F*-value	*p*-Value
Stim	1.23	0.28	0.02	0.90	0.85	0.37	0.03	0.87
Orient	0.32	0.58	0.01	0.91	0.22	0.65	1.61	0.22
Partic	0.11	0.74	3.56	0.08	2.14	0.16	0.13	0.72
Stim × Orient	0.91	0.35	0.92	0.35	0.37	0.55	3.01	0.10
Stim × Partic	0.11	0.75	0.18	0.67	0.15	0.70	0.03	0.87
Orient × Partic	5.69	**<0.05**	1.42	0.25	0.26	0.62	0.05	0.82
Stim × Orient × Partic	9.23	**<0.01**	2.64	0.12	0.48	0.50	0.03	0.88

Bold values indicate significance.

were not consciously perceived. Consistent with our prediction, the SFE was not found in the early visual processing of adults with HFASD, whereas the SFE was observed in TD adults. More specifically, TD adults exhibited enhanced neural activity in response to fearful faces presented at sub-threshold compared with objects ("emotion effect"), reflected in the earliest VEP component (N1). To our knowledge, this is the first neurophysiological evidence for altered early visual processing of briefly perceived emotional faces in individuals with ASD, consistent with the findings reported in behavioral studies (Hall, West, & Szatmari, 2007; Kamio et al., 2006a).

The observed group difference in the N1 response pattern cannot be explained by attention levels, since the target detection task revealed that adults with HFASD did not differ from TD adults in either behavioral performance or P300 responses to the target stimuli. Therefore, we suggest that the distinct neural response observed in the V1 of TD adults was specific to perception of fearful faces in our study.

3.1. "Subliminal face effect" in TD

The TD group demonstrated a fearful face-specific SFE under the upright condition. This can be explained by the effect of low SF information on faces. Itier and Taylor (2004) proposed that low-level spatial information is critical in discriminating faces from objects. For instance, images of fearful faces with a low SF elicited a larger P1 relative to neutral faces with a low SF, while this emotional effect was not observed in high SF faces (Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005). In humans, visual images containing low and high SF information are processed by distinct neural channels. The magnocellular channel is responsible for processing low SF (holistic) information (Tobimatsu & Celesia, 2006). Therefore, the observed increase in N1 in response to upright fearful faces in TD adults may reflect activation of the magnocellular system within the V1. This system may work to enable the rapid identification of upright fearful faces.

It is possible that subcortical fast face processing contributed to the observed alterations in the N1 in our study because the upright SFE was specific to fearful faces ("emotion effect"). The subcortical system involved in the non-conscious