World Journal of Psychiatry

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5498/wjp.v4.i2.42

World J Psychiatr 2014 June 22; 4(2): 42-48
ISSN 2220-3206 (online)

CASE CONTROL STUDY

Cognitive inflexibility in Japanese adolescents and adults with autism spectrum disorders

Yuka Yasuda, Ryota Hashimoto, Kazutaka Ohi, Hidenaga Yamamori, Michiko Fujimoto, Satomi Umeda-Yano, Haruo Fujino, Masatoshi Takeda

Yuka Yasuda, Kazutaka Ohi, Michiko Fujimoto, Masatoshi Takeda, Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka 5650871, Japan
Ryota Hashimoto, Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Osaka 5650871, Japan
Ryota Hashimoto, Hidenaga Yamamori, 2nd Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka 5650871, Japan
Hidenaga Yamamori, Satomi Umeda-Yano, Department of Molecular Neuropsychiatry, Osaka University Graduate School of Medicine, Osaka 5650871, Japan
Haruo Fujino, Graduate School of Human Sciences, Osaka University, Osaka 5650871, Japan
Author contributions: Yasuda Y was critically involved in the data collection and analysis, wrote the first draft of the manuscript, and contributed intellectually to the interpretation of the data; Hahimoto R supervised the entire project, collected the data, wrote the manuscript, was critically involved in the design of the project and was responsible for performing the literature review; all authors were critically involved in the data collection and helped to edit the manuscript.
Supported by Research grants from the Japanese Ministry of Health, Labor and Welfare, No. H22-seishin-ippan-001; the Japan Society for the Promotion of Science (JSPS) through a Grant-in-Aid for Scientific Research, No. 22390225, No. 25293250 and No. 24591680; Challenging Exploratory Research, No. 23659565; the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) through a Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network), No. 25129704; Priority Areas-Research on the Pathomechanisms of Brain Disorders, No. 18023045; and the Japan Foundation for Neuroscience and Mental Health
Correspondence to: Ryota Hashimoto, MD, PhD, Associate Professor, Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, D3, 2-2, Yamadaoka, Suita, Osaka 5650871, Japan. hashimor@psy.med.osaka-u.ac.jp
Telephone: +81-6-68793074 **Fax:** +81-6-68793074
Received: November 22, 2013 **Revised:** February 17, 2014
Accepted: April 11, 2014
Published online: June 22, 2014

Abstract

AIM: To investigate executive function in Japanese adolescents and adults with autism spectrum disorders (ASD) compared to Japanese controls.

METHODS: Thirty-three individuals with ASD and 33 controls participated. The ASD and control groups' demographic variables were matched for gender (male/female: 20/13 *vs* 20/13), age (26.1 ± 11.5 *vs* 26.8 ± 9.6), years of education (13.2 ± 2.9 *vs* 14.2 ± 1.9), full-scale intelligence quotient (IQ) (103.0 ± 16.7 *vs* 103.7 ± 14.7), performance IQ (96.2 ± 16.1 *vs* 97.8 ± 15.0), and verbal IQ (107.9 ± 16.3 *vs* 107.7 ± 14.4). Participants performed the Wisconsin Card Sorting Test (WCST), which assesses the executive processes involved in problem solving and cognitive flexibility, and the Continuous Performance Test (CPT), which assesses attention and impulsivity. Symptoms were assessed by the Autism-Spectrum Quotient Japanese version (AQ-J). First, we compared the scores of the WCST between the groups using a Mann-Whitney *U*-test and conducted an analysis of covariance for the variables with the scores of category archives and CPT scores as covariates. Second, we analyzed the correlation between the scores of the WCST and the AQ-J in the ASD group using Pearson's r.

RESULTS: The total errors (TE) and the percentages of perseverative errors of the Milner type (%PEM) and Nelson type (%PEN) among the TE in the ASD group were significantly worse compared with the control group (ASD *vs* Control, respectively: TE: 16.0 ± 6.2 *vs* 12.6 ± 3.5, $P = 0.012$; %PEM: 11.7 ± 10.7 *vs* 6.6 ± 8.9, $P = 0.037$; %PEN: 20.1 ± 14.5 *vs* 8.7 ± 10.4, $P = 0.0011$). In contrast, no significant difference was observed between the two groups in the scores of categories achieved on the WCST or the CPT. An analysis of covariance revealed significant differences between the groups in the %PEN scores ($P = 0.0062$) but not in the TE or the %PEM scores. These results suggest that Japanese adolescents and adults with ASD have cognitive inflexibility. Furthermore, our results suggest that Japanese adolescents and adults with ASD may have difficulties using negative feedback because perseverative errors of the Nelson type indicate persistence in choosing the incorrect reaction. By contrast, there was no significant correlation between the WCST and AQ-J scores.

CONCLUSION: We confirmed the presence of cognitive inflexibility in Japanese adolescents and adults with ASD. Our results also indicated that subjects with ASD may not use negative feedback effectively.

Key words: Executive function; Autism spectrum disorders; Perseverative errors of Nelson type; Negative feedback; Wisconsin Card Sorting Test

Core tip: We investigated executive function (EF) in Japanese adolescents and adults with autism spectrum disorders (ASD) compared to strictly matched controls. EF was assessed using the Wisconsin Card Sorting Test. To exclude confounding factors, the participants were matched for gender, age, years of education, full-scale intelligence quotient (IQ), performance IQ, verbal IQ, and attention level. Symptoms were assessed by the Autism-Spectrum Quotient Japanese version. We confirm that Japanese adolescents and adults with ASD have cognitive inflexibility, as suggested by previous findings. Furthermore, the present study results also indicate that subjects with ASD may not use negative feedback effectively.

Yasuda Y, Hashimoto R, Ohi K, Yamamori H, Fujimoto M, Umeda-Yano S, Fujino H, Takeda M. Cognitive inflexibility in Japanese adolescents and adults with autism spectrum disorders. *World J Psychiatr* 2014; 4(2): 42-48 Available from: URL: http://www.wjgnet.com/2220-3206/full/v4/i2/42.htm DOI: http://dx.doi.org/10.5498/wjp.v4.i2.42

INTRODUCTION

Autism spectrum disorders (ASD), also known as pervasive developmental disorders (PDD), are defined, according to Text Revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-Ⅳ-TR), as severe and pervasive impairments in the development of reciprocal social interactions and verbal and nonverbal communication skills as well as stereotyped behavior, interests, and activities. Over the past decade, the prevalence rate of ASD has risen to 0.2%-1.0% worldwide[1]. However, the neural basis of ASD remains poorly understood. Recently, the new DSM-5 diagnostic criteria were published. One of the most important differences in ASD between the old and new criteria is the narrower diagnosis under the DSM-5 compared to the DSM-Ⅳ-TR. According to the DSM-5, the prevalence of ASD is lower than that reported in the DSM-Ⅳ-TR[2].

The neuropsychological explanation of ASD is at an intermediate level between the brain and behavior. Three key neuropsychological domains have been proposed as key cognitive disabilities to explain the phenotype of ASD[3,4]: social cognition, central coherence, and executive function. Restricted and repetitive behaviors and interests have been proposed to be closely associated with executive dysfunctions in individuals with ASD[3,5]. Executive functions refer to a variety of functions, such as planning, working memory, impulse control, inhibition, and cognitive flexibility[6]. Each function can be assessed by various tasks. Among these tasks, the Wisconsin Card Sorting Test (WCST)[7] is one of the most distinctive tests of cognitive flexibility impairments[8]. In previous studies, children with autism were highly perseverative on this task compared to typical developmental controls and to children with other developmental disorders, such as attention deficit hyperactivity disorder (ADHD), language disorder, Tourette syndrome, and dyslexia[9,10]. Some studies have reported no significant difference in perseverative errors on the WCST after controlling for verbal functioning[11,12]. These findings suggest that perseverative tendencies may be related to verbal ability. Other studies have reported normal perseverative performance in individuals of average intelligence with autism[13,14]. However, this opinion is controversial[15]. Some studies have reported executive differences between subjects with ASD and ADHD. ADHD is primarily defined by inattention, hyperactivity, and impulsivity (DSM-Ⅳ-TR, DSM-5). Both ASD and ADHD involve executive function (EF) deficits, and individuals with ASD often show ADHD symptoms[16]. In one study, the ASD group exhibited significant impairments in initiation, planning, and strategy formation[17]. In contrast, the ADHD group had difficulty withholding a response, with relative preservation of initiation and planning abilities[17]. The ASD group with ADHD was found to have more problems in inhibitory performance but not in the working memory task compared to the ASD group without ADHD symptoms[18]. The combination of ASD and ADHD has also been associated with poorer attention than ASD alone[19]. Thus, ADHD symptoms have been suggested to have an additive effect on EF.

Because subjects with ASD often show attention deficits, we assessed the attention levels of the participants by using the Continuous Performance Test (CPT). In addition, years of education and the version of the WCST used can influence the WCST[20]. The original WCST required subjects to use communication skills related to verbal and non-verbal task demands by the tester. Compared to the original WCST, the computerized task has been reported to be easier for subjects with ASD because it reduces social task demands by the tester[8,12]. Previous findings have shown that children with ASD made more preservation errors on a controlled task-switching variant of the WCST[6]. Thus, cognitive flexibility may

Table 1 Demographic information for subjects with autism spectrum disorders and controls

	ASD (n = 33)	Control (n = 33)	P value
Sex (male/female)	20/13	20/13	χ^2 (1, n = 66) = 1.00 P = 1.00
Age (yr)	26.1 (11.5)	26.8 (9.6)	U = 459.0, Z = -1.10 P = 0.27
Age range (yr)	15-63	18-61	
Education years	13.2 (2.9)	14.2 (1.9)	U = 441.0, Z = -1.35 P = 0.18
FIQ	103.0 (16.7)	103.7 (14.7)	U = 534.0, Z = -0.13 P = 0.89
PIQ	96.2 (16.1)	97.8 (15.0)	U = 495.5, Z = -0.63 P = 0.53
VIQ	107.9 (16.3)	107.7 (14.4)	U = 521.0, Z = -0.30 P = 0.76
CPT mean D′ score	3.10 (0.61)	3.38 (0.53)	U = 396.0, Z = -1.90 P = 0.057

Data are represented as the mean ± SD and P value. Differences in clinical characteristics were analyzed using the χ^2 test for gender and the Mann-Whitney U-test for the other variables. ASD: Autism spectrum disorders; IQ: Intelligence quotient; FIQ: Full-scale IQ; PIQ: Performance IQ; VIQ: Verbal IQ; CPT: Continuous Performance Test.

be confounded by intelligence, verbal functioning, years of education, attention level, and task demands. To our knowledge, there are no reports in Japan that compare subjects with ASD to controls who are strictly matched for these confounding factors. Therefore, to reduce the influence of these confounding factors, we investigated cognitive flexibility between individuals with ASD and controls matched for gender, age, education years, attention level, full-scale intelligence quotient (IQ) (FIQ), verbal IQ (VIQ), and performance IQ (PIQ). We used a computerized version of the WCST to reduce social task demands.

Adolescents and adults participated in our study because the diagnosis of ASD has recently become more widespread, and the cognitive characteristics of adolescents and adults with ASD are not well known[21]. Symptoms of ASD are thought to be maintained throughout life. Therefore, the investigation of cognitive characteristics in various life stages is very important for treatment[21]. Another benefit to studying the cognitive characteristics of both adolescents and adults is to avoid results based on individual developmental variation.

MATERIALS AND METHODS

Subjects

The study cohort consisted of 33 patients with ASD and 33 healthy controls. All participants were Japanese. We obtained data on patients with ASD and healthy controls from the research bio-resource of the Human Brain Phenotype Consortium in Japan (http://www.sp-web.sakura.ne.jp/consortium.html). The ASD and control groups' demographic variables were matched for age, gender, education years, FIQ, VIQ, and PIQ (Table 1). Patients with ASD were recruited from both outpatient and inpatient services at Osaka University Hospital. Each ASD patient was diagnosed by at least two trained child psychiatrists according to the criteria in the DSM-Ⅳ-TR. Diagnoses were based on unstructured or semi-structured behavioral observations of the patients and interviews with the patients and their parents or caregivers, as described previously[22]. In addition, ASD criteria on the Autism Diagnostic Interview-Revised[23], the Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS)[24], and the Autism-Spectrum Quotient Japanese version (AQ-J)[25] were used to assist in the evaluation of ASD-specific behaviors and symptoms. The PARS is a semi-structured interview that is composed of 57 questions in eight domains of the characteristics of children with PDD. This interview was developed by the Autism Society of Japan. Four subjects met the full criteria for autistic disorder, 15 subjects met the criteria for Asperger's disorder, and 14 subjects met the criteria for PDD Not Otherwise Specified. Among the patients with ASD, none of the subjects had a low IQ (< 70). The medications taken by the participants with ASD at the time of testing were as follows: 18 participants were free of medication, nine participants were treated with antipsychotics (mean CPZ equivalent: 240.0 mg/d; range: 25-750 mg/d), five participants were treated with antidepressants and/or other drugs, and one participant had an unknown medication regimen.

A detailed description of the healthy controls has been provided in previous reports[26]. Briefly, the controls were biologically unrelated Japanese subjects. Healthy controls were screened using the structured clinical interview for the DSM-5 Axis I disorders. Subjects were excluded if they had neurological or medical conditions that could potentially affect the central nervous system, had any psychiatric diseases and/or received psychiatric medication, had first- or second-degree relatives with a psychiatric disease, or presented with an IQ less than 70.

Following a description of the study, written informed consent was obtained from each subject. This study was conducted in accordance with the World Medical Association's Declaration of Helsinki and was approved by the ethics committee at Osaka University.

Cognitive tests

Wechsler Adult Intelligence Scale-Ⅲ: The IQ data for all subjects were measured using the Japanese version of the full-scale Wechsler Adult Intelligence Scale-Ⅲ[27].

Computerized WCST

All participants completed a computerized version of the Computerized WCST, the Keio Version[28]. The computerized version can eliminate the social task demands required in the original version, including verbal and nonverbal communications with the tester. The WCST consists of four stimulus cards and 48 response cards with geometric figures that vary according to three perceptual dimensions (color, form, or number). The task requires subjects to find the correct classification principle by trial

Table 2 Performance on the Wisconsin Card Sorting Test in subjects with autism spectrum disorders and controls

	ASD (n = 33)	Control (n = 33)	P value
CA	4.76 (1.28)	5.24 (0.90)	U = 433.5, Z = -1.51 P = 0.13
TE	16.03 (6.24)	12.61 (3.52)	U = 350.0, Z = -2.51 P = 0.012[a]
%PEM	11.69 (10.72)	6.58 (8.87)	U = 389.0, Z = -2.09 P = 0.037[a]
%PEN	20.09 (14.54)	8.74 (10.41)	U = 294.0, Z = -3.26 P = 0.0011[a]

Data are represented as the mean ± SD, [a]P < 0.05 *vs* control; differences in the clinical characteristics were analyzed using the Mann-Whitney U-test. ASD: Autism spectrum disorders; CA: Categories achieved; TE: Total number of errors; %PEM: Percentages of perseverative errors of the Milner type; %PEN: Percentages of perseverative errors of the Nelson type.

and error and computer feedback. This means that there are no indications that a switch occurred or knowledge about the rules that should be applied. Following sequences of six consecutive correct matches, the classification principle changes without warning. We analyzed the outcome measures as follows: the number of categories achieved (CA), the total errors (TE), the percentage of TE for perseverative errors of the Milner type (%PEM), and the percentage of TE for perseverative errors of the Nelson type (%PEN). The CA consists of the number of sequences of six consecutive correct matches. The PEM is the total number of incorrect responses following the category concept that was previously answered correctly. The PEN is the total number of incorrect responses in the same category as the immediately preceding incorrect response.

Continuous performance test

Attention in all subjects was measured using the Continuous Performance Test-Identical Pairs version (CPT-IP), as described previously[29]. CPT-IP is a computerized version of the test. Participants were required to focus on a computer screen that presented various two- to four-digit numbers for a short duration. The participants were instructed to maintain a finger press on the mouse and only respond by lifting the finger when two identical stimuli appeared on consecutive trials. A signal detection index, *D*', is the most commonly studied variable of the CPT-IP; it is considered a relatively pure measure of sustained attention because it controls for response bias. Therefore, the parameter *D*' was used as the outcome variable representing a measure of sensitivity composed of hits and false alarms. *D*' 2, *D*' 3, and *D*' 4 correspond to the number of digits in each number. A high score of *D*' indicates high performance. We compared the mean scores of *D*' 2, *D*' 3, and *D*' 4 between ASD subjects and controls (Table 1).

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 16.0 (SPSS Japan Inc., Tokyo, Japan). Group comparisons of demographic data and performance data were performed using a χ^2 test for categorical variables and a Mann-Whitney U-test for continuous variables. Because we observed tendencies toward reduced performance in the CA and reduced mean *D*' score of the CPT in individuals with ASD compared to the controls, we conducted an analysis of covariance (ANCOVA) for the WCST indices with the scores of the CA and the mean *D*' score as covariates. To investigate the effects of AQ-J and IQ scores on performance in the WCST, Pearson's r was used to correlate performance scores with IQ for each variable. This analysis was conducted separately for the control group and the ASD group. All P values reported are two-tailed. Statistical significance was defined as P < 0.05.

RESULTS

Descriptive statistics

There were no significant differences in gender, age, education years, FIQ, VIQ, or PIQ between the groups (ASD *vs* control, respectively, for each variable: male/female: 20/13 *vs* 20/13, χ^2 (1, n = 66) = 1.00, P = 1.00; age: 26.1 ± 11.5 *vs* 26.8 ± 9.6, U = 459.0, z = -1.10, P = 0.27; age range: 15-63 *vs* 18-61; education years: 13.2 ± 2.9 *vs* 14.2 ± 1.9, U = 441.0, z = -1.35, P = 0.18; FIQ: 103.0 ± 16.7 *vs* 103.7 ± 14.7, U = 534.0, z = -0.13, P = 0.89; PIQ: 96.2 ± 16.1 *vs* 97.8 ± 15.0, U = 495.5, z = -0.63, P = 0.53; VIQ: 107.9 ± 16.3 *vs* 107.7 ± 14.4, U = 521.0, z = -0.30, P = 0.76) (Table 1). Subjects with ASD had significantly higher total scores on the AQ-J compared to controls (ASD: 31.73 ± 7.54, Control: 18.88 ± 6.35, U = 62, z = -4.96, $P = 6.8 \times 10^{-7}$).

Attention level

We found that the mean *D*' scores of the CPT tended to be lower in the ASD group compared with the controls (ASD: 3.10 ± 0.61, Control: 3.38 ± 0.53, U = 396.0, z = -1.90, P = 0.057) (Table 1). We used *D*' scores on the CPT as covariates for the analysis of cognitive flexibility.

Cognitive flexibility

Compared to the controls, subjects with ASD performed worse in the WCST categories, including the TE (ASD: 16.03 ± 6.24, Control: 12.61 ± 3.52, U = 350.0, z = -2.51, P = 0.012), the %PEM (ASD: 11.69 ± 10.72, Control: 6.58 ± 8.87, U = 389.0, z = -2.09, P = 0.037), and the %PEN (ASD: 20.09 ± 14.54, Control: 8.74 ± 10.41, U = 294.0, z = -3.26, P = 0.0011) (Table 2). No significant difference was found in the CA scores between the groups (ASD: 4.76 ± 1.28, Control: 5.24 ± 0.90, U = 433.5, z = -1.51, P = 0.13) (Table 2). CA and attention may influence the performance of subjects on the WCST. Thus, we conducted an analysis of covariance (ANCOVA) for the three disturbed WCST variables with the mean *D*' scores of the CPT and the CA as covariates to control for confounding factors. An ANCOVA revealed a significant difference in the %PEN between the two groups ($F_{1,62}$ =

Table 3 Correlation between intelligence quotient and performance on the Wisconsin Card Sorting Test in subjects with autism spectrum disorders and controls

	ASD (n = 34)						Control (n = 34)					
	FIQ		VIQ		PIQ		FIQ		VIQ		PIQ	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
CA	0.24	0.18	0.26	0.20	0.15	0.260	0.22	0.220	0.19	0.29	0.20	0.27
TE	-0.26	0.15	-0.19	0.28	-0.31	0.084	-0.30	0.089	-0.28	0.12	-0.25	0.16
%PEM	-0.26	0.14	-0.23	0.20	-0.26	0.140	-0.31	0.082	-0.32	0.073	-0.22	0.22
%PEN	-0.41	0.019[a]	-0.42	0.015[a]	-0.32	0.068	-0.31	0.076	-0.28	0.11	-0.27	0.14

[a]P < 0.05 *vs* control, Pearson's r was used to correlate performance scores with intelligence quotient for each variable. ASD: Autism spectrum disorders; CA: Categories achieved; TE: Total number of errors; %PEM: Percentages of perseverative errors of the Milner type; %PEN: Percentages of perseverative errors of the Nelson type; IQ: Intelligence quotient; FIQ: Full-scale IQ; PIQ: Performance IQ; VIQ: Verbal IQ.

8.04, P = 0.0062), whereas no significant differences were found in the TE or the %PEM between the groups (TE: $F_{1,62}$ = 3.36, P = 0.072, %PEM: $F_{1,62}$ = 1.37, P = 0.25). These results suggest that adolescents and adults with ASD made more perseverative errors of the Nelson type than the controls.

Correlations between intelligence and cognitive flexibility

We investigated correlations between IQ scores and scores on the WCST (Supp 1). There were weak negative correlations between the %PEN and the FIQ or the VIQ (FIQ: r = -0.41, P = 0.019, VIQ: r = -0.42, P = 0.015), whereas there were no significant correlations between IQ scores (PIQ, VIQ, or FIQ) and the other measurements of the WCST in the subjects with ASD. There were no significant correlations between scores on the three domains of IQ (FIQ, VIQ, and PIQ) and the measurements of the WCST in the controls. These results suggest that verbal function may negatively correlate with the %PEN on the WCST in Japanese adolescents and adults with ASD.

Correlations between AQ-J score and cognitive flexibility

We investigated correlations between scores on the AQ-J and the WCST in subjects with ASD. There was no significant difference between the total scores of the ASD group and the control group (CA: r = 0.0065, P = 0.97, TE: r = 0.57, P = 0.78, %PEM: r = 0.12, P = 0.50, %PEN: r = 0.012, P = 0.95). There was no correlation between the subscores of the ASD group and the control group (data not shown) (Table 3).

DISCUSSION

The aim of this study was to investigate cognitive flexibility in Japanese adolescents and adults with ASD. To exclude the possible impact of several factors on cognitive flexibility, we recruited controls matched for age, gender ratio, education years, attention level, FIQ, PIQ, and VIQ.

In our study, the TE, the %PEM, and the %PEN in the WCST were significantly higher in the Japanese adolescents and adults with ASD compared with the controls. However, we did not observe a significant difference in the CA between the two groups. These results were consistent with previous reports in Caucasians[3,12]. In some reports, the CA in subjects with ASD was higher compared with controls[9,12,30]. The inconsistency between studies may be due to variation in illness, the treatment of patients, and/or differences in the version of the WCST used. We did not find significant differences in the CA between the two groups; this may be due to the older age of our cohort compared to earlier studies in which the CA was correlated with age[20].

When we controlled for the CA as a confounding factor, we found that only %PEN remained significantly disturbed. The %PEN represents situations in which the participants do not change their incorrect responses even after they know the response is wrong. The %PEN indicates deficits in using negative feedback effectively. Because subjects with ASD often show attention impairments, we investigated the attention level of subjects with ASD in our study. Although there was no significant difference in the score of the CPT between the groups, subjects with ASD had a lower attention level than the controls in our study (P = 0.057). The results did not change after an ANCOVA for scores on the CPT. These results suggest that Japanese adolescents and adults with ASD may have low effectiveness in using negative feedback. Therefore, deficits in using negative feedback may be one of the core mechanisms related to cognitive inflexibility in subjects with ASD.

After statistically controlling for verbal abilities, significant differences were not found in some reports[10,12]. These findings suggest that verbal disabilities negatively correlate with cognitive flexibility. Our examination of the relationship between cognitive flexibility and the VIQ in the ASD group revealed that the %PEN was negatively correlated with the VIQ. This finding suggests that a low verbal IQ may lead to a prediction of cognitive inflexibility in subjects with ASD.

Our data highlight the cognitive flexibility of high-functioning individuals. Perseverative performance on the WCST was consistent with previous studies, which have reported normal mental flexibility for children with ASD of average intelligence[13,14] or who were matched to controls on the basis of verbal functioning[10-12]. However, many studies have found cognitive inflexibility in normal-

IQ individuals with ASD[6,15,30]. In the present study, we confirmed the presence of cognitive inflexibility in subjects with a normal IQ similar to the low-IQ (< 70) individuals. This result suggests that cognitive flexibility may depend on some confounding factors, such as years of education, attention levels, and task demands.

Scores on the AQ-J were not correlated with cognitive flexibility in our study. This result is consistent with previous findings[31,32]. Our result might suggest that cognitive flexibility measured by the WCST does not reflect social adaptation in the real world. Alternatively, this lack of correlation may be because the cases in our study were not severe enough to be initially diagnosed in childhood. The subjects who could not complete the AQ-J because of their persistence in the questions were excluded. Therefore, the participants in the analysis of the correlation between scores on the AQ-J and the WCST may not have severe deficits in EF. This is the primary limitation of this study.

Another limitation of the present study is the wide age range distribution. Although we matched the cases and controls for age, gender, education years, attention levels, FIQ, PIQ, and VIQ, we cannot deny the influence of these factors. Because our sample size was relatively small, studies with larger sample sizes are necessary to draw a firm conclusion.

We confirmed the presence of cognitive inflexibility in Japanese adolescents and adults with ASD in strictly matched samples. Our results also showed deficits in the usage of negative feedback in subjects with ASD. Recent brain imaging studies have shown widespread activation across frontal and non-frontal brain regions during WCST performance[8]. Our findings may be consistent with impairments of prefrontal function in ASD as a key node within the widely distributed and tightly interconnected neural networks related to human cognition.

ACKNOWLEDGMENTS

We thank every individual who participated in this study.

COMMENTS

Background

Autism spectrum disorders (ASD), also known as pervasive developmental disorders, are defined, according to Text Revision of the Diagnostic and Statistical Manual of Mental Disorders, as severe and pervasive impairments in the development of reciprocal social interactions and verbal and nonverbal communication skills as well as stereotyped behavior, interests, and activities.

Research frontiers

There are no reports in Japan that compare subjects with ASD to controls that are strictly matched for these confounding factors.

Innovations and breakthroughs

To reduce the influence of these confounding factors, this investigated cognitive flexibility between individuals with ASD and controls matched for gender, age, education years, attention level, full-scale intelligence quotient (IQ), verbal IQ, and performance IQ. This used a computerized version of the Wisconsin Card Sorting Test to reduce social task demands.

Applications

The investigation of cognitive characteristics in various life stages is very important for treatment. Another benefit to studying the cognitive characteristics of both adolescents and adults is to avoid results based on individual developmental variation.

Peer review

The authors proposed to compare the cognitive flexibility between ASD and healthy controls matched by age, education level. The study design was well-conducted. The results in this study could provide clinical evidence to understand what cognitive inflexibility in ASD.

REFERENCES

1 **Levy SE**, Mandell DS, Schultz RT. Autism. *Lancet* 2009; **374**: 1627-1638 [PMID: 19819542 DOI: 10.1016/S0140-6736(09)61376-3]

2 **Maenner MJ**, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, Van Naarden Braun K, Kirby RS, Bakian AV, Durkin MS. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. *JAMA Psychiatry* 2014; **71**: 292-300 [PMID: 24452504 DOI: 10.1001/jamapsychiatry.2013.3893]

3 **Hill EL**. Executive dysfunction in autism. *Trends Cogn Sci* 2004; **8**: 26-32 [PMID: 14697400]

4 **Losh M**, Adolphs R, Poe MD, Couture S, Penn D, Baranek GT, Piven J. Neuropsychological profile of autism and the broad autism phenotype. *Arch Gen Psychiatry* 2009; **66**: 518-526 [PMID: 19414711 DOI: 10.1001/archgenpsychiatry.2009.34]

5 **Johnson MH**. Executive function and developmental disorders: the flip side of the coin. *Trends Cogn Sci* 2012; **16**: 454-457 [PMID: 22835639 DOI: 10.1016/j.tics.2012.07.001]

6 **Van Eylen L**, Boets B, Steyaert J, Evers K, Wagemans J, Noens I. Cognitive flexibility in autism spectrum disorder: Explaining the inconsistencies? *Res Autism Spectr Disord* 2011; **5**: 1390-1401 [DOI: 10.1016/j.rasd.2011.01.025]

7 **Heaton RK**, Chelune GJ, Talley JL, Kay GG, Curtiss G. Wisconsin Card Sorting Test Manual: Revised and expanded. Odessa: Psychological Assesment Resources Inc., 1993

8 **Nyhus E**, Barceló F. The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: a critical update. *Brain Cogn* 2009; **71**: 437-451 [PMID: 19375839 DOI: 10.1016/j.bandc.2009.03.005]

9 **Pascualvaca DM**, Fantie BD, Papageorgiou M, Mirsky AF. Attentional capacities in children with autism: is there a general deficit in shifting focus? *J Autism Dev Disord* 1998; **28**: 467-478 [PMID: 9932233]

10 **Robinson S**, Goddard L, Dritschel B, Wisley M, Howlin P. Executive functions in children with autism spectrum disorders. *Brain Cogn* 2009; **71**: 362-368 [PMID: 19628325 DOI: 10.1016/j.bandc.2009.06.007]

11 **Liss M**, Fein D, Allen D, Dunn M, Feinstein C, Morris R, Waterhouse L, Rapin I. Executive functioning in high-functioning children with autism. *J Child Psychol Psychiatry* 2001; **42**: 261-270 [PMID: 11280422]

12 **Lopez BR**, Lincoln AJ, Ozonoff S, Lai Z. Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder. *J Autism Dev Disord* 2005; **35**: 445-460 [PMID: 16134030 DOI: 10.1007/s10803-005-5035-x]

13 **Ozonoff S**, Miller JN. Teaching theory of mind: a new approach to social skills training for individuals with autism. *J Autism Dev Disord* 1995; **25**: 415-433 [PMID: 7592252]

14 **Rumsey JM**. Conceptual problem-solving in highly verbal, nonretarded autistic men. *J Autism Dev Disord* 1985; **15**: 23-36 [PMID: 3980427]

15 **Minshew NJ**, Goldstein G, Muenz LR, Payton JB. Neuropsychological functioning in nonmentally retarded autistic individuals. *J Clin Exp Neuropsychol* 1992; **14**: 749-761 [PMID: 1474143 DOI: 10.1080/01688639208402860]

16 **Matson JL**, Rieske RD, Williams LW. The relationship between autism spectrum disorders and attention-deficit/hyperactivity disorder: an overview. *Res Dev Disabil* 2013; **34**:

2475-2484 [PMID: 23751293 DOI: 10.1016/j.ridd.2013.05.021]
17 **Bramham J**, Ambery F, Young S, Morris R, Russell A, Xenitidis K, Asherson P, Murphy D. Executive functioning differences between adults with attention deficit hyperactivity disorder and autistic spectrum disorder in initiation, planning and strategy formation. *Autism* 2009; **13**: 245-264 [PMID: 19369387 DOI: 10.1177/1362361309103790]
18 **Sinzig J**, Morsch D, Bruning N, Schmidt MH, Lehmkuhl G. Inhibition, flexibility, working memory and planning in autism spectrum disorders with and without comorbid ADHD-symptoms. *Child Adolesc Psychiatry Ment Health* 2008; **2**: 4 [PMID: 18237439 DOI: 10.1186/1753-2000-2-4]
19 **Lundervold AJ**, Stickert M, Hysing M, Sørensen L, Gillberg C, Posserud MB. Attention Deficits in Children With Combined Autism and ADHD: A CPT Study. *J Atten Disord* 2012; Epub ahead of print [PMID: 22940852 DOI: 10.1177/1087054712453168]
20 **Rhodes MG**. Age-related differences in performance on the Wisconsin card sorting test: a meta-analytic review. *Psychol Aging* 2004; **19**: 482-494 [PMID: 15382998 DOI: 10.1037/0882-7974.19.3.482]
21 **Geurts HM**, Vissers ME. Elderly with autism: executive functions and memory. *J Autism Dev Disord* 2012; **42**: 665-675 [PMID: 21656030 DOI: 10.1007/s10803-011-1291-0]
22 **Yasuda Y**, Hashimoto R, Yamamori H, Ohi K, Fukumoto M, Umeda-Yano S, Mohri I, Ito A, Taniike M, Takeda M. Gene expression analysis in lymphoblasts derived from patients with autism spectrum disorder. *Mol Autism* 2011; **2**: 9 [PMID: 21615902 DOI: 10.1186/2040-2392-2-9]
23 **Lord C**, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994; **24**: 659-685 [PMID: 7814313]
24 **Yamada A**, Suzuki M, Kato M, Suzuki M, Tanaka S, Shindo T, Taketani K, Akechi T, Furukawa TA. Emotional distress and its correlates among parents of children with pervasive developmental disorders. *Psychiatry Clin Neurosci* 2007; **61**: 651-657 [PMID: 18081627 DOI: 10.1111/j.1440-1819.2007.01736.x]
25 **Wakabayashi A**, Tojo Y, Baron-Cohen S, Wheelwright S. [The Autism-Spectrum Quotient (AQ) Japanese version: evidence from high-functioning clinical group and normal adults]. *Shinrigaku Kenkyu* 2004; **75**: 78-84 [PMID: 15724518]
26 **Yasuda Y**, Hashimoto R, Ohi K, Fukumoto M, Takamura H, Iike N, Yoshida T, Hayashi N, Takahashi H, Yamamori H, Morihara T, Tagami S, Okochi M, Tanaka T, Kudo T, Kamino K, Ishii R, Iwase M, Kazui H, Takeda M. Association study of KIBRA gene with memory performance in a Japanese population. *World J Biol Psychiatry* 2010; **11**: 852-857 [PMID: 20509760 DOI: 10.3109/15622971003797258]
27 **Wechsler D**. Wechsler Adult Intelligence Scale - Third Edition, Manual. San Antonio, TX: The Psychological Corporation, 1997
28 **Kashima H**, Handa T, Kato M, Yokoyama N, Murakami M, Muramatsu T, Saito S, Onoe Y, Mimura M, Asai M, Hosaki H. Neuropsychological investigation on chronic schizophrenia-Aspects of its frontal functions. Amsterdam: Elsevier Science Publishers, 1987
29 **Ohi K**, Hashimoto R, Yasuda Y, Fukumoto M, Nemoto K, Ohnishi T, Yamamori H, Takahashi H, Iike N, Kamino K, Yoshida T, Azechi M, Ikezawa K, Tanimukai H, Tagami S, Morihara T, Okochi M, Tanaka T, Kudo T, Iwase M, Kazui H, Takeda M. The AKT1 gene is associated with attention and brain morphology in schizophrenia. *World J Biol Psychiatry* 2013; **14**: 100-113 [PMID: 22150081 DOI: 10.3109/15622975.2011.591826]
30 **Sumiyoshi C**, Kawakubo Y, Suga M, Sumiyoshi T, Kasai K. Impaired ability to organize information in individuals with autism spectrum disorders and their siblings. *Neurosci Res* 2011; **69**: 252-257 [PMID: 21129422 DOI: 10.1016/j.neures.2010.11.007]
31 **Dichter GS**, Radonovich KJ, Turner-Brown LM, Lam KS, Holtzclaw TN, Bodfish JW. Performance of children with autism spectrum disorders on the dimension-change card sort task. *J Autism Dev Disord* 2010; **40**: 448-456 [PMID: 19890707 DOI: 10.1007/s10803-009-0886-1]
32 **Faja S**, Dawson G. Performance on the dimensional change card sort and backward digit span by young children with autism without intellectual disability. *Child Neuropsychol* 2013; Epub ahead of print [PMID: 24266398 DOI: 10.1080/09297049.2013.856395]

P- Reviewers: Ladislav H, Lu RB, Philip H **S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com