

February 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7520-review.doc).

Title: Cognitive inflexibility in Japanese adolescents and adults with autism spectrum disorders

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

Name of Journal: *World Journal of Psychiatry*

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The manuscript has been improved according to the suggestions of the reviewers:

1 The format has been updated.

2 Revisions have been made according to the suggestions of the reviewers.

Reviewed by 02445219

(1) Why is the CPT not mentioned in the introduction, results (table) and discussion section.

→According to the reviewer's suggestion, we now discuss the CPT in the introduction, results (table), and discussion section on the following pages:

In the introduction section (p.7, l.14-p.7, l.15);

Because subjects with ASD often show attention deficits, we assessed the attention levels of the participants using the Continuous Performance Test (CPT).

In the results section (p.13, l.13-p.13, l.15);

Attention level

We found that the mean D' scores of the CPT tended to be lower in the ASD group compared to 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 the D' scores of the CPT as a covariate for the analysis of cognitive flexibility.

In the discussion section (p.15, l.20–p.16, l.2);

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.

(2) The WAIS-III should be mentioned before the WCST in the methods section.

→According to the reviewer's suggestion, we now discuss the WAIS-III (p.10, l.13–p.10, l.15) before the WCST (p.10, l.17–p.11, l.9) in the materials and methods section.

(3) The manuscript gives almost no information on ASD and general neuropsychological findings which are important in this special research field. One should not only focus on the WCST.

→According to the reviewer's suggestion, we now include additional information on ASD in the materials and methods section as follows:

In the introduction section (p.6, ℓ.12–p.6, ℓ.20);

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].

(4) What new information is provided by this study?

→According to the reviewer's suggestion, we now clearly describe the new information gained from our study in the discussion section as follows:

In the introduction section (p.7, ℓ.22–p.8, ℓ.4);

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 IQ (FIQ), verbal IQ (VIQ), and performance IQ (PIQ). We used a computerized version of the WCST to reduce social task demands.

Reviewed by 00426994

- (5) Overall, some grammatical errors in the manuscript may confuse readers, the authors are recommended to ask for a native-English editor

→According to the reviewer's suggestions, the paper was edited by a professional native English speaker in NPG Language Editing suggested by this journal.

- (6) In Introduction, several studies have been demonstrated the cognitive inflexibility in ASD, the authors should have a comprehensive review to give a rationale of how their study could contribute more. References: Bramham, J., Ambery, F., Young, S., Morris, R., Russell, A., Xenitidis, K., . . . Murphy, D. (2009). Executive functioning differences between adults with attention deficit hyperactivity disorder and autistic spectrum disorder in initiation, planning and strategy formation. *Autism*, 13(3), 245-264. doi:10.1177/1362361309103790. Sinzig, J., Morsch, D., Bruning, N., Schmidt, M., & Lehmkuhl, G. (2008). Inhibition, flexibility, working memory and planning in autism spectrum disorders with and without comorbid ADHD-symptoms. *Child and Adolescent Psychiatry and Mental Health*, 2(1), 4. Van Eylen, L., Boets, B., Steyaert, J., Evers, K., Wagemans, J., & Noens, I. (2011). Cognitive flexibility in autism spectrum disorder: Explaining the inconsistencies? *Research in Autism Spectrum Disorders*, 5(4), 1390-1401. doi: <http://dx.doi.org/10.1016/j.rasd.2011.01.025>

→According to the reviewer's suggestions, we have cited these papers and additional papers as follows:

In the introduction section

(p.7, l.5-p.7, l.13);

Both ASD and ADHD involve 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.

(p.7, l.19-p.7, l.21);

Previous findings have shown that children with ASD made more preservation errors on a controlled task-switching variant of the WCST ^[6].

- (7) Although previous studies in ASD were focused on children, the authors should make their rationale and importance of studying in adolescents and adults compared to matched normal controls.

→According to the reviewer's suggestion, we now discuss the rationale and importance of studying both adolescents and adults in our study as follows:

In the introduction section

(p.8, l.5-p.8, l.10);

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.

- (8) The WCST has been well-established to examine the executive function in ASD, either computerized or original one. The authors should review such information in more details.

→According to the reviewer's suggestion, we now discuss the computerized WCST in more detail in the introduction section as follows:

In the introduction section (p.7, l.15-p.7, l.21);

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].

(9) Although the authors compared the matched ASD and controls and found no significant differences in IQs, the ASD group the authors recruited might be high-functioning or with normal IQ. The authors should discuss this comparison in Discussion section.

→According to the reviewer's suggestion, we now discuss the comparison in the discussion section as follows:

Discussion section (p.16, l.12-p.16, l.19):

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.

Reviewed by 02445209

(10) Abstract: It seems strange that there is no Introduction/Background section in your abstract.

→ BPG's Revision Policies for Brief Articles indicates that the structured abstract should

consist of the aim, methods, results, and conclusion. Therefore, we provided the background in the introduction section.

(11) Introduction - the 4th line from above: You quote DSM-IV, but DSM-V has already been published in May 2013, it would be better to quote DSM-V.

→According to the reviewer's suggestion, we now discuss the DSM-V in the introduction section as follows:

In the introduction section (p.6, l.2-p.6, l.10);

Autism spectrum disorders (ASD), also known as pervasive developmental disorders (PDD), are defined 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 (DSM-IV-TR). Over the past decade, the prevalence rate of ASD has risen to 0.2% - 1.0% worldwide [1]. However, the brain basis of ASD remains poorly understood. Recently, the new DSM-5 diagnostic criteria were published. One of the most important differences for 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 that reported in the DSM-IV-TR [2].

(12) Table 2 - remarks below the table: I do not understand your statement "Differences in the clinical characteristics were analyzed using the chi-square test for gender..." The data in the Table 2 seems not to be related to gender of the study subjects.

→According to the reviewer's suggestion, we corrected the table legend in the Table 2 as follows:

Table 2 (p.21)

Differences in the clinical characteristics were analyzed using the Mann-Whitney *U*-test for the variables.

(13)Suppl 1: I do not understand the statement below the table "Data are represented as the mean plus minus SD." I do not see any means or SDs in the table, only rs and p values are present.

→According to the reviewer's suggestion, we corrected the table legend in Suppl. 1 as follows:

Suppl 1 (p.22)

ASD: autism spectrum disorders. WCST: Wisconsin Card Sorting Test. CA: categories achieved. TE: total numbers of errors. %PEM: % perseverative errors of Milner. %PEN: % perseverative errors of Nelson. * $P < 0.05$. Pearson's r was used to correlate performance scores with IQ for each variable. scores with IQ for each variable.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Psychiatry.

Sincerely yours,

A handwritten signature in black ink on a light-colored background. The signature is cursive and appears to read 'Ryota Hashimoto'.

Ryota Hashimoto, MD, PhD

Molecular Research Center for Children's Mental Development

United Graduate School of Child Development, Osaka University

D3, 2-2, Yamadaoka, Suita, Osaka

565-0871, Japan

Fax: +81-6-6879-3074

E-mail: hashimor@psy.med.osaka-u.ac.jp