## PPI IN CHILDREN AND DEVELOPMENTAL DISORDERS

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

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

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

## CONCLUSION

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

### Acknowledgments

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

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

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Running Head: Switching Attention in Asperger's Disorder

# 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

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.

Fig. 1 about here

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 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 degrees in width, and local stimuli subtended 0.4 × 0.3 degrees. All stimuli were displayed at the center of the monitor, and were drawn in white on a gray background (see Fig. 2).

Fig. 2 about here

### *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 1000 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).

Table 1 about here

*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).

Fig. 3 and Fig. 4 about here

*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 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).

Fig. 5 about here

## 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 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