Fronto-limbic Functioning in Children and Adolescents With and Without Autism

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Abstract

We used neuropsychological tasks to investigate integrity of brain circuits linking orbitofrontal cortex and amygdala (orbitofrontal-amygdala), and dorsolateral prefrontal cortex and hippocampus (dorsolateral prefrontal-hippocampus), in 138 individuals aged 7 – 18 years, with and without autism. We predicted that performance on orbitofrontal-amygdala tasks would be poorer in the Autism group compared to the Non-Autism group regardless of intellectual level (verbal mental age – VMA) and that performance on dorsolateral prefrontal-hippocampus tasks would be associated primarily with intellectual level. Predicted differences between Autism and Non-Autism groups on orbitofrontal-amygdala tasks were present but greater in individuals with higher VMA. On dorsolateral prefrontal-hippocampus tasks, poorer performance by the Autism compared to the Non-Autism group was found at all VMA levels. Group differences suggest both brain circuits are impaired in autism, but performance on all tasks is also associated with intellectual level.

Recent human studies using behavioral and neuroimaging techniques, as well as studies using animal models, have provided numerous clues to the underlying structural and functional brain changes associated with autistic spectrum disorders (hereafter, *autism*). Children and adults with autism have been shown to have developmental abnormalities and functional impairment of the frontal lobe, medial temporal structures, and cerebellum, as reflected in histopathology, structural and functional neuroimaging, electrophysiology, and neuropsychological studies (see for review, Bachevalier & Loveland, 2003). However, because autism is developmental in nature, it is unlikely to be based in focal abnormalities of any single neural structure or region, but instead is more likely to be distributed in neural networks. Consequently, developmental brain abnormalities in autism would be expected to affect brain circuits and the interaction of brain regions both during behavior and over the course of development. Two

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brain regions have repeatedly been implicated in autism: the prefrontal and medial temporal regions. These two regions are heavily interconnected and form two neural networks that appear to be critical for the monitoring of social cognition, executive functions, and episodic memory (see for review Bachevalier & Loveland, 2006).

Based on the characteristics of their anatomical connections, the prefrontal-temporal networks have been subdivided into two subsystems (Barbas, 1995; Goldman-Rakic, 1988). One of these systems is a ventral circuit centered around the amygdala and includes the anterior cingulate and orbital frontal cortex, and temporal pole. This ventral circuit has been implicated in the monitoring of emotional states and social cognition as well as in the self-regulation of behavior through knowledge of emotional responses and intentions of others (Barbas, 1995; Baron-Cohen et al., 1999; Brothers, 1989, 1995). The second is a dorsal subsystem, which is centered around the hippocampus and comprises the parahippocampal, posterior cingulate, parietal, and dorsolateral prefrontal cortices. This dorsal network monitors the on-line processing of events and actions in the service of the visuospatial domain and memory. Evidence that links both subsystems to autism has increased in the last two decades.

The Orbitofrontal-Amygdala Circuit

Involvement of the amygdala and orbital frontal cortex (the ventral network) in autism has recently been extensively reviewed (Bachevalier & Loveland, 2006). The data suggest that, although the amygdala does not generate specific emotional responses such as fear, it codes and processes facial movements, eye-gaze direction, body postures, and gestures that are important in production and modulation of appropriate social and emotional responses (see Adolphs, 2003). The amygdala is also implicated in a specific class of stimulus-reward associations (see Baxter & Murray, 2000). By contrast, the orbital frontal cortex is less important for identifying the reward value of stimuli, but rather contributes to the anticipation of reward and adjusts behavioral responses in accordance with changing contexts (Bechara, Damasio, Damasio, & Anderson, 1994). Thus, after damage to the orbital frontal cortex, the failure to adapt behavior when reinforcers have changed may be a fundamental deficit that underlies impulsiveness, disinhibition, and inappropriate social-emotional behavior (Bechara, Damasio, Damasio, & Lee, 1999; see for review Holland & Gallagher, 2004). This process of self-regulation is of special importance to the social-emotional cognition and behavior of persons with autism.

Given the specific roles of the amygdala and orbital frontal cortex in self-regulation, we can make several predictions. A dysfunction of the amygdala might result in difficulty detecting information relevant to the mental states, emotions, attitudes and intentions of others and their significance for oneself. By contrast, a dysfunction of the orbital frontal cortex would result in difficulty modifying one's own behavior appropriately in response to changes in the behavior of others. Like individuals with partial damage to the amygdala (Young, Hellawell, Van de Wakl, & Johnson, 1996), people with autism often perform poorly in identifying faces and facial expressions, discrimination of faces, and memory for faces (for review see Dalton et al., 2005; Dawson et al., 2005; Jemel et al., 2006; Loveland, 2005; Sasson, 2006; Schultz, 2005), and they lack insight into the mental life of other individuals (Baron-Cohen, 1995). Further, people with autism are less able to use such information to guide their own behavior. Thus, they also resemble individuals with damage to the orbital frontal cortex, who have difficulty modulating goal-directed behaviors in response to changes.

The Dorsolateral-Prefrontal-Hippocampus Circuit

Considering the dorsal frontal-limbic network, the hippocampus and adjacent cortical areas on the parahippocampal gyrus have been found to be critical for semantic and episodic or relational memory (Eichenbaum, 2001; Lavenex & Amaral, 2000; Mishkin, Suzuki, Gadian, & Vargha-

Khadem, 1997; O'Reilly & Rudy, 2001; Squire & Zola-Morgan, 1996). Conversely, source memory, executive functions, and particularly spatial working memory, are subserved by a distributed brain network in which the dorsal prefrontal cortex plays a pivotal role (Goldman-Rakic, 1988). These two brain regions within the dorsal network have also been suggested to be dysfunctional in autism.

Since the early reports of Hermelin and O'Connor (1970) and Boucher and Warrington (1976) that noted similarities between autism and adult-onset temporal amnesia, several studies of memory processes in individuals with autism have provided controversial results (see for review Ben Shalom, 2003). For example, DeLong (1992) suggested that autism relates to an early dysfunction of the hippocampus. However, more recent studies have shown that perinatal damage to the hippocampus in children yields a profound episodic memory impairment, sparing semantic memory processes (Vargha-Khadem et al., 1997), but does not result in autism. Nevertheless, a number of reports found that individuals with autism showed normal, or near normal performance, in recognition and free recall tasks (Bennetto, Pennington, & Rogers, 1996; Minshew & Goldstein, 1993; Renner, Klinger, & Klinger, 2000), but impaired performance on tasks measuring episodic memory (Boucher, 1981; Boucher & Lewis, 1989; Boucher, Cowell, Howard, Broks, Farrant, Roberts, & Mayes, 2005; Bowler, Gardiner, & Grice, 2000; Klein, Chan, & Loftus, 1999; Millward, Powell, Messer, & Jordan, 2000; Toichi & Kamio, 2003). Similarly, there has been no consistent report of changes in hippocampal volumes in autism (for review see Cody, Pelphrey, & Piven, 2002). Nevertheless, postmortem investigations of the brains of people with autism (Bauman & Kemper, 2004) demonstrated reduced neuronal cell size and increased cell-packing density bilaterally in the hippocampus.

Neurobiological and functional abnormalities have been found in the dorsolateral prefrontal region of individuals with autism (Carper & Courchesne, 2000; Harrison, Demaree, Shenal, & Everhart, 1998; Kawasaki, Yokota, Shinomiya, Shimizu, & Niwa, 1997). Using SPECT, reduced metabolism in prefrontal cortex (Ohnishi et al., 2000) and delayed maturation of frontal circuitry (Zilbovicius et al., 1995) were found in these individuals. Further, functional disconnectivity of frontal cortex with other cortical and subcortical regions has been demonstrated using [18]-fluorodeoxyglucose PET (Horwitz, Rumsey, Grady, & Rapoport, 1988). fMRI studies have indicated a decreased frontal activation in persons with autism during the processing of social stimuli (Baron-Cohen et al., 1999) and complex spatial stimuli, as in the embedded figures task (Ring et al., 1999). More recently, Minshew, Luna, and Sweeney (1999) and Minshew, Meyer, and Goldstein (2002) found that persons with autism had significant deficits in the accuracy of saccades made to remembered locations as assessed by an oculomotor delayed response task, a deficit associated with a decreased activation in prefrontal and posterior cingulate circuitry (Luna, Minshew, Garver, Lazar, Thulborn, Eddy & Sweeney, 2002). Similar eye movement abnormalities suggestive of a spatial working memory deficit were found in parents of individuals with autism (Koczat, Rogers, Pennington, & Ross, 2002). Finally, a number of studies provide support for a role of the dorsolateral prefrontal cortex in the behavioral and cognitive manifestations of autism, and some of these studies have suggested that such deficits are associated with deficits in performance on Theory-of-Mind tasks (Coldren & Halloran, 2003; Craig & Baron-Cohen, 1999; Dawson, Klinger, Panagiotides, Lewy, & Castelloe, 1995; Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002; McEvoy, Rogers, & Pennington, 1993; Ozonoff, 1995; Ozonoff, Pennington, & Rogers, 1991). Yet there is also evidence to suggest that executive function deficits are not specific to autism spectrum disorders (Baron-Cohen & Robertson, 1995; Griffith, Pennington, Wehner, & Rogers, 1999; Ozonoff, 1997; Pennington et al., 1997; Sergeant, Geurts, & Oosterlaan, 2002) and some executive functioning deficits can be reduced or absent in the highest functioning individuals, especially those with Asperger syndrome (Liss et al., 2001; Rinehart, Bradshaw, Moss, Brereton, & Tonge, 2001). Similar findings were also reported in a study demonstrating intact working memory in high-

functioning individuals with autism (Ozonoff & Strayer, 2001). Rather than being a general deficit, the performance of persons with autism on tasks of executive functioning appears to be tied closely to the specific task used, and the kinds of functions it taps (cf Kleinhas, Akshoomoff & Delis, 2005).

Although a dysfunction of these two fronto-limbic subsystems has been implicated in autism, the data are still controversial and sometimes contradictory. Some of the underlying problems with the studies described above are that the functioning of these two neural systems has been investigated in different samples of individuals with autism and controls, and in most of the studies the autism group included only older, higher-functioning individuals with a limited range of developmental levels. Thus little is known about the functioning of these systems in persons with intellectual disability, with or without autism. Studies have also used differing neuropsychological measures, thus rendering comparisons across studies very difficult. Additionally, most of the earlier studies lacked a specific hypothesis that explains not only the symptoms associated with autism, but their heterogeneity and their developmental time course.

An earlier report (Bachevalier, 1991) of an animal model of autism indicated that combined neonatal damage to the amygdala, hippocampus, and adjacent parahippocampal cortex are the critical determinants of autistic behavior. Subsequent work on this animal model (Bachevalier, 1994) suggested that the amygdala is likely to be involved together with the orbital frontal cortex in the social dysfunction of autism, but that the hippocampus together with the dorsolateral prefrontal cortex may only be involved when additional impairments of language acquisition and cognitive abilities are present (see also Bachevalier & Loveland, 2006; Boucher et al., 2005). Thus, the study reported here was part of a program of research to investigate two main hypotheses: 1) that the primary social-emotional and social-cognitive deficits of autism are related to developmental dysfunction of the orbitofrontal-amygdala circuit, and 2) that intellectual disability in autism is associated with dysfunction of the dorsolateral prefrontal-hippocampus circuit.

A preliminary study (Loveland, Bachevalier, Nemanic, & Pearson, 2001) comparing children and adolescents with and without autism aged 6 to 19 years was conducted using the four neuropsychological tasks employed in the present study (Object Discrimination Reversal, Delayed Non-Match-to-Sample, Memory Span, and Spatial Delayed Alternation). We hypothesized that impairment of the orbitofrontal-amygdala circuit is characteristic of persons with autism regardless of IQ, but that impairment of the dorsolateral prefrontal-hippocampus circuit is characteristic primarily of persons with autism and lower IQ. The study found deficits on tasks tapping the orbitofrontal-amygdala circuit in both higher and lower IQ participants with autism, compared with non-autism controls of similar age and IQ, suggesting that differences on these tasks are present regardless of intellectual level. However, we did not find differences by diagnosis in tasks tapping the dorsolateral prefrontal-hippocampus circuit, suggesting that performance on these tasks is more closely related to degree of intellectual disability than to autism.

Following the preliminary study, we undertook a larger and better-controlled study to investigate the integrity of these two brain circuits in persons with and without autism using neuropsychological tasks listed above. Comparable groups of children and adolescents with and without autism (ages 7 to 18) with a wide range of intellectual functioning in each group (Verbal IQ 36 – 124) were compared. Based on our preliminary findings we predicted that 1) performance on tasks measuring functioning of the orbitofrontal-amygdala circuit would be poorer in the Autism group as compared to the Non-Autism group across levels of intellectual development and 2) that performance on tasks measuring functioning of the dorsolateral prefrontal-hippocampus circuit would differ primarily by level of intellectual development and only to a lesser extent by autism diagnosis. In order to address our hypotheses, we examined

not only group differences in performance on the neuropsychological tasks, but also the contribution of intellectual level to performance.

Methods

Participants

Male and female children and adolescents aged 7 to 18 years with autism (Autism group: n = 80) and without autism (Non-Autism group: n = 58) participated. All participants were recruited from the research database of our research center and from community referrals. All received the Stanford-Binet Intelligence Test, 4th Edition, the Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore, & Risi, 1999) and the Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994). All participants and their parents gave informed consent prior to participation, unless the individual was judged to be too young or developmentally delayed to do so. In such cases parents gave informed consent and their children gave child's assent following an oral explanation. This research was reviewed and approved by the Internal Review Board for human subjects research of the University of Texas Health Science Center at Houston and was performed in accordance with accepted ethical standards.

The groups were recruited to be comparable in verbal IQ (VIQ), nonverbal IQ, Verbal Mental Age (VMA), sex and age, and in the distributions of these characteristics (see Table 1). For our analyses we selected Verbal MA as the measure of level of intellectual development because past research has shown that differences in verbal skills can sometimes account for performance differences between persons with and without autism (cf Hobson, 1991). Mental age rather than IQ was used because we wished to separate the effects of chronological age and mental age, whereas IQ is adjusted for age norms. Thus, recruitment of Autism and Non-Autism groups that are similar in VMA and VIQ as well as chronological age results in a more conservative test of hypotheses (e.g., see Hobson, 1991 for discussion of these methodological points). Verbal MA for each individual was derived by calculating the median age equivalent score in months for the subscales of the Stanford-Binet Verbal Reasoning Scale.

Participants in the Autism group met ADI-R algorithm criteria for Autistic Disorder. The ADI-R was administered to caregivers of all potential participants by an experienced clinician who was trained to administer this instrument reliably by two licensed psychologists (KL and DAP). Most participants in the Autism group also currently met criteria for autism based on the ADOS. A few individuals recruited for the Autism group met ADI-R algorithm criteria for an autism spectrum disorder but not ADOS criteria. These cases were reviewed individually by two qualified clinicians (KL and DAP) who were trained to reliability on the ADI-R and ADOS by the authors of these instruments (Dr. Catherine Lord and colleagues). Cases of this kind were excluded unless there was agreement between both clinicians that the ADOS results were not representative of the individual's usual behavior and that there was strong evidence indicating that a diagnosis of Autistic Disorder was warranted. In the final sample there were 8 such participants included in the Autism group. Potential participants in the Non-Autism group were excluded if they had a history of diagnosed or probable significant psychiatric illness, such as depression or other mood disorder, or psychosis, or if there were significant risk factors for such disorders, such as a known history of trauma or abuse, as determined from parent interview. Individuals with a history of neurological disorders (e.g., head trauma, brain tumor, known illnesses or uncontrolled seizures) were also excluded. Potential participants referred for either group were excluded if they had possible signs of an autistic spectrum disorder (for example, evidence of repetitive behaviors, obsessions or compulsions or unusual social behaviors) but did not actually meet ADI-R criteria for autism. Data from the seven individuals recruited for the Non-Autism group who were excluded for partial or possible overlap with the autism spectrum are not reported in this paper.

Procedures

All participants received four neuropsychological tasks (Object Discrimination Reversal, Delayed Non-Match-to-Sample, Memory Span, and Spatial Delayed Alternation) designed to assess functioning of the neural circuits of interest. All tasks were selected based on prior human and animal studies indicating their sensitivity in detecting subtle dysfunction in the four brain regions to be investigated. All tasks were derived from neuropsychological testing in nonhuman primates and were designed to avoid the need for verbal instructions, insuring that all participants could perform on all tasks at a mental-age appropriate level. To examine the functioning of the orbitofrontal-amygdala circuit, we used an Object Discrimination Reversal task to measure response inhibition and shifts in strategy and a Delayed Non-Match-to-Sample task to measure discrimination of Facial Expressions and Facial Identity (with control task Object Identity), respectively. For the functioning of the dorsolateral prefrontal-hippocampus circuit, we used a Spatial Memory Span task (with control task Object Memory Span) to measure spatial recognition memory and a Spatial Delayed Alternation task to measure spatial working memory, respectively. Tasks were given to each participant in the following order: Object Discrimination Reversal, Delayed Non-Match to Sample, Spatial Memory Span, and Spatial Delayed Alternation. This order of administration was necessary to minimize the effects of interference among tasks. The tasks are illustrated in Figure 1.

Apparatus and reward

Tasks were given in a quiet room by two experimenters, one who administered the tasks and the other who sat close to the participant and helped him or her to remain focused. All tasks were given in one day with several breaks to enhance participants' motivation and attention.

Tasks were administered using a table top version of the Wisconsin General Testing Apparatus (WGTA). The WGTA had a wooden partition with a movable screen which could be raised to allow the participant to choose stimuli placed on a test tray or lowered to obstruct the view of the tray when the experimenter positioned the stimuli and rewards on each trial. The test tray had three recessed wells in which rewards could be hidden, except in the Memory Span task, for which the test tray had 19 wells.

Reward preference was determined in advance for each participant: M&M's, Skittles candies, Goldfish crackers, or pennies. Participants were told that they would play games during which they would discover where the reward was hidden. They could either have the rewards during the game or save them for later in a bag. Most chose to save the rewards for later. Because no verbal instructions were given, participants had to learn by trial and error the rule governing each task. At the end of each task, the participant was told that the game was over and that a new game would begin. The tasks are described in the order they were administered.

One-Pair Object Discrimination Reversal task—The One Pair Object Discrimination Reversal task began with a discrimination phase that required the participant to make a consistent choice between two toy objects (for example, a yellow bucket and a black car). On the first trial, the two objects were placed over the two lateral wells with a reward under both. The object selected on the first trial was the one that would conceal the reward for the remaining trials in the discrimination phase. The left/right position of the objects on the lateral wells of the testing tray was pseudorandomized across trials. Training continued until the participant selected the car on five consecutive trials or to a maximum of 30 trials. Once the criterion was met, a reversal occurred, during which the reward was placed under the other object without the participant's knowledge. Trials continued in this way until the participant displaced the bucket for 5 consecutive trials, at which point the object to be rewarded was again changed for another reversal. Participants received 6 such reversals. Total number of errors for the initial discrimination phase and for each reversal was calculated for each person.

For participants who could not reach the criterion of 5 successive correct choices within the maximum of 30 trials in the discrimination phase, the task was continued using a correction procedure. After an incorrect choice, the trial was presented repeatedly until the participant retrieved the reward. If the criterion was still not met with correction trials, the Object Discrimination Reversal was temporarily discontinued in favor of other tasks. The participant was later re-trained on the Object Discrimination Reversal task using two new objects after all other tasks were given. This second testing on the Object Discrimination Reversal task was done to insure that poor performance was not due to difficulty adapting to the type of task, since Object Discrimination Reversal was the first task given using the WGTA.

Five Concurrent Pairs Object Discrimination Reversal task—Because early piloting suggested that older and more intellectually able participants might find the One-Pair Object Discrimination Reversal task too easy, we also used a task with five pairs. This task was given only to participants who scored only 1 or 2 errors in two successive reversals on the One-Pair Object Discrimination Reversal task, indicating that they had attained mastery of it over the course of the reversals. Those who did not reach this criterion were not given the Five-Pair Object Discrimination Reversal task. The procedure was the same as in the one pair version, except that *pictures of objects* were used instead of real objects. The participant first received the discrimination phase to learn which picture in each of the five pairs was rewarded. For this phase, the set of five pairs of object pictures were presented repeatedly until the participant chose the five rewarded pictures of the set consecutively. Without warning, the examiner changed the reward values of each pair of pictures (Reversal 1), so that for each, the rewarded picture became unrewarded. The set of five pairs of pictures was again presented until the participant displaced the five rewarded pictures of the set consecutively, after which Reversals 2 through 6 were given in the same way. The task was discontinued if the participant could not learn the initial discrimination of the five pairs.

Delayed Non-Match-to-Sample task—This task was selected to measure discrimination of three different types of pictures, i.e. objects (Object Identity condition), different faces with neutral expression (Facial Identity condition), or the same person with different facial expressions (Facial Expression condition). Before beginning the task, participants received a *pretraining phase* in which they learned by trial and error the non-matching rule governing the Delayed Non-Match-to-Sample task. For the training phase, three-dimensional objects differing in shape, color and size were used. Each trial consisted of a sample presentation in which a reward was placed into the central well and covered with an object. The screen was raised and the participant was allowed to displace the object to get the reward. The screen was then lowered for 5 s, and during this short delay, the familiar object and a new one were positioned over the two lateral wells with the reward under the new object. The screen was raised again and the participant chose between the two objects, either retrieving or not retrieving the reward. The screen was then lowered for a 10 s intertrial interval, after which a second trial was presented in exactly the same way, but with a pair of new objects. Pre-training continued in this way with new objects on each trial until the participant made 5 correct responses in a row, demonstrating that the non-matching rule was learned, or to a maximum of 30 trials.

The task was then continued using pictures instead of objects. Each condition (object identity, facial identity, and facial expression) was administered in succession, using a new pair of objects in each trial until the participant made 5 correct responses in a row or to a maximum of 20 trials for each condition. Number of errors in each condition was the dependent measure.

Spatial Memory Span and Object Memory Span tasks—This pair of tasks was administered next because they use the same non-matching rule as the Delayed Non-Match-to-Sample task above. A 19-well tray was used for both conditions. The Object Memory Span (control condition) was given first. Nineteen unique objects were used to cover the 19 wells

one at a time. On the first trial, a reward was placed in one of the wells and covered with an object. The screen was raised and the participant displaced the object and retrieved the reward. The screen was then lowered for a 30 s delay during which the object was put back in place, and a reward was put in a different well and covered with a new object. Because a new object was added to the tray on each trial, the participant had to locate and displace the newest object on the testing tray. The task was discontinued when the participant made three consecutive errors. For the Spatial Memory Span condition, a similar procedure was used, with 19 identical green plaques instead of the 19 objects. In this condition, the participant had to identify the newest plaque on the basis of its location on the tray. For both the Object Memory Span and the Spatial Memory Span tasks, the number of wells covered before reaching the criterion of three consecutive errors was the dependent measure.

Spatial Delayed Alternation task—A 3-well tray was used and two identical green plaques covered the lateral wells on each trial. On the first trial, rewards were placed in both lateral wells and covered with plaques. The screen was raised and the participant was allowed to select one plaque and get the reward. The screen was then lowered for a 20 s intertrial interval. In the next trial, only the well not chosen on the first trial held a reward. On the following trials, rewards alternated from one well to the other (left-right-left-right, etc…). A correction procedure was given when the participant displaced the incorrect plaque; the two wells were covered by the plaques and the participant was allowed to choose again repeatedly (with a 5 s intertrial interval) until s/he displaced the correct plaque and retrieved the reward. The task then resumed alternating the reward from one well to the other until the participant made 5 correct responses in a row or reached a maximum of 30 trials, not counting correction runs. Number of errors before reaching the criterion was used as the dependent measure.

Results

All statistical analyses were done with SPSS for Windows version 14.0 GLM and JMP-IN for Macintosh OSX. We examined the effects of Group, VMA, and the Group x VMA interaction for each task using a general linear model analysis. Because VMA may not fully control for the effect of developmental level, we began by testing a model that included the three above-mentioned effects as well as Age and the Age x Group interaction. Because these latter effects were not found to be significant, they were removed from the model and the analysis was run with just the Group, VMA, and the Group x VMA interaction variables. When the Group x VMA interaction was not significant, then it too was dropped from the model. A number of our cognitive task variables had very non-normal distributions (skew). To increase the power and validity of ANOVA, variables were transformed to produce approximately normal distributions, using the Tukey ladder of transformations (Winer, 1971). Inferential statistics are all reported on the transformed variables, however, for ease of interpretation, the untransformed means and standard deviations are also reported in the text and illustrated in Figure 2 – Figure 8

Tasks Examining the Orbitofrontal-Amygdala Circuit

Object Discrimination Reversal Tasks—All participants were able to complete the One-Pair Object Discrimination Reversal task, except 12 cases who could not learn the first discrimination and who received a second testing with two new objects after all other tasks were given. In 6 of 12 instances, participants receiving the second version of the 1-pair Object Discrimination Reversal task did not improve their performance and so their first testing data was used. In the remaining 6 cases, the data from the second One-pair Object Discrimination Reversal was used for the statistical analyses.

The initial model for the One-Pair Object Discrimination Reversal task was the same as for other tasks except that the additional within-subjects factor "reversals" was included. The multivariate approach to repeated measures was used. In the final model, the effect of VMA was significant, $F(1, 134) = 18.74$, $p < 0.001$. No other effects approached significance. Thus, performance on One-Pair Object Discrimination Reversal was related primarily to VMA, and this relationship was the same for both groups (Figure 2).

Because not all participants performed well enough on the One-Pair Object Discrimination Reversal to receive the Five-Pair version, the total number receiving the more difficult version of the task was smaller (n=81). As would be expected, the subset who received the Five-Pair Object Discrimination Reversal was somewhat higher in VIQ, NVIQ and age than the sample as a whole (Table 1). The analysis for the Five-Pair Object Discrimination Reversal was the same as for One-Pair version. There were no group differences in the mean number of errors made while learning the 5-pair discrimination. As can be seen in Figure 3, the Autism group made more errors overall than did the Non-Autism group. The effect of Group was significant, $F(1, 78) = 7.94$, $p = 0.006$. Figure 3 also shows that the mean errors from Reversal 1 to Reversal 2 increased in the Autism group, but decreased slightly in Non-Autism group. This pattern was reflected in a significant Group x Reversals interaction, $F(5, 74) = 3.75$, $p = 0.004$.

Delayed Non-Match to Sample Tasks—Mean errors on the Object Picture condition was highly skewed, so a $\frac{-1}{\sqrt{X+1}}$ transformation was applied. The mean score for the Autism group (M = −0.687, SD = 0.223) was very close to that for the Non-Autism group (M = −0.690, SD = 0.216). None of the effects approached significance in any of the models. These results suggest that children and adolescents with and without autism perform similarly when discriminating non-social stimuli.

On the Facial Identity condition, a square root transformation was applied to the number of errors to reduce skew. The slope for the Non-Autism group was steeper (b = −0.012) than the slope for the Autism group (b = −0.009), with both slopes significantly lower than 0, $p < 0.001$. However, the difference in slopes did not approach significance, $F < 1$. The Non-Autism group made significantly fewer errors (M = 0.64, SD = 0.70) in the highest quartile of VMA than did the Autism group (M = 1.31, SD = 0.71), $F(1, 30) = 9.12$, $p = 0.005$. The difference between groups did not approach significance in any of the other quartiles, $p > 0.30$.

On the Facial Expression condition a square root transformation was applied to the mean number of errors to reduce skew. As in the Facial Identity condition, the slope of the relationship was 50% steeper for the Non-Autism group than for the Autism group. The difference in slopes shown in Figure 4 was reflected in a significant Group x VMA interaction, $F(1, 133) = 4.90$, $p = 0.029$. Each slope was significantly lower than 0, $p < 0.001$. Significance tests of the difference between groups were conducted for each of the four quartiles of VMA. The Non-Autism group made significantly fewer errors (M = 0.46, SD = 0.70) in the highest quartile of VMA than did the Autism group (M = 1.31, SD = 0.87). The difference between groups did not approach significance in any other quartiles.

Figure 5 illustrates the mean errors to criterion for the pre-training phase using 3-D objects and for the three experimental conditions by diagnosis. There were no group differences in the pre-training phase, indicating that all participants mastered the Delayed Non-Match-to-Sample rule.

Tasks Examining the Dorsolateral Prefrontal-Hippocampal Circuit

Spatial Memory Span Task—In order to control for the possibility that group differences on the Spatial Memory Span were due to differences in the ability to perform any span-type

task and to reduce error variance, all models included the span score from the control task (Object Memory Span) as a covariate. We believe this statistical control is prudent even though the Autism (M = 16.34, SD = 3.80) and Non-Autism groups (M = 16.81, SD = 3.60) made the same number of errors on the Object Span (see Figure 6). Figure 7 shows box plots of mean Spatial Memory Span error score for the Autism and the Non-Autism groups with the data adjusted for VMA. The Non-Autism group did considerably better. The median for the Non-Autism group corresponded approximately to the 75th percentile of the Autism group, and the 25th percentile of the Non-Autism group was higher than the median for the Autism group. The effects of Group, $F(1, 133) = 16.50$, $p < 0.001$, VMA, b = 0.036, F(1, 133) 33.23, $p < 0.001$, and mean Object Memory Span score, $b = 0.411$, $F(1,133) = 20.51$, $p < 0.001$ were significant. The group difference in Spatial Memory Span performance can be interpreted in terms of the number of months of VMA that would produce the same effect size as the adjusted mean group difference of 2.76. Specifically, given that the slope of the relationship between VMA and Spatial Memory Span was 0.036, this difference of 2.76 corresponds to 2.76/0.036 = 76.6 months. In other words, individuals in the Non-Autism group would be expected to score at about the same level on Spatial Memory Span as those in the Autism group with a mean VMA 76.6 months higher. Thus, individuals in the Autism group needed a verbal mental age nearly 6 ½ years greater than that of the Non-autism group to "overcome" the detrimental effects on task performance of having autism.

Spatial Delayed Alternation Task—A log(X+1) transformation was done to reduce skew (Figure 8). The Autism group made significantly more errors (adjusted M = 1.66) than the Non-Autism group (adjusted M = 1.12), $F(1, 134) = 7.44$, $p = 0.007$. The pooled error standard deviation was 1.13 so the difference between means is 0.47 standard deviations. VMA was negatively significantly related to errors, $b = -0.008$, $F(1,134) = 20.26$, $p < 0.001$. Thus, both groups performed better with increasing VMA.

Discussion

In the section to follow, we first discuss the results of each task, and then consider how these results reflect upon the hypotheses.

Tasks Measuring Functions of the Orbitofrontal-Amygdala Circuit

Adapting Responses to Changing Reward Value—Results suggested that the Autism group may have had greater difficulty than the Non-Autism group in reversing learned behavioral responses in the Object Discrimination Reversal task. On the less-challenging One-Pair version, the groups did not differ significantly, but performance was positively associated with developmental level (VMA). On the Five-Pair Object Discrimination Reversal, the Autism group on average consistently made more errors across reversals. The difference in performance between the groups was smallest on reversal 1, but it diverged quickly at the second reversal and thereafter. The pattern of impairment found in the Autism group mirrors the pattern of impairment generally found on the Object Discrimination Reversal task following damage to the orbital frontal cortex. Thus, Butter (1968) found that monkeys with damage to the orbital frontal cortex, but not those with lesions of the dorsolateral prefrontal cortex, made more errors than controls on the first reversal, but the difference was not significant. However, they made significantly more errors than controls in subsequent reversals (see also Izquierdo, Suda, & Murray, 2004 for similar results). In addition, converging evidence from brain damage in humans and from human functional neuroimaging studies has demonstrated that the orbital frontal cortex plays a critical role in reversal learning (see for review Bachevalier & Loveland, 2006; Clark, Cools, & Robbins, 2004). More importantly, impairment in object reversal learning also follows neonatal damage to the orbital frontal cortex in monkeys (see for review Goldman-Rakic, Isseroff, Schwartz, & Bugbee, 1983) suggesting that dysfunction of the orbital

frontal cortex could occur in early infancy in people with autism. This proposal is supported by recent volumetric studies (Girgis, Minshew, Melhem, Nutche, Keshavan, & Hardan, 2007; Hardan, Girgis, Lacerda, Yorbik, Kilpatrick, Keshavan, & Minshew, in press) demonstrating decreased volume of the right lateral orbital frontal cortex (white plus grey matter) in people with autism, and in one of these studies (Girgis et al., 2007) the changes were correlated with social deficits.

Discrimination of Facial Identity and Facial Expressions—Discrimination of facial identity and facial emotional expressions, but not of objects, was poorer overall in persons with autism. However, participants with lower VMA in both the Autism and Non-Autism groups performed similarly on the Facial Expression condition, whereas with higher VMA their mean performance increasingly diverged (see Figure 4). The same pattern was found for the Facial Identity condition, in that higher VMA was more strongly associated with better performance in the Non-Autism group than in the Autism group. Interestingly, in the Object Pictures condition, performance was similar for higher VMA individuals in the Autism and Non-Autism groups. Thus, performance of persons with autism was poorer in discriminating facial-affective stimuli than non-social stimuli, indicating that group differences were probably not due to difficulty applying the Delayed Non-Match-to-Sample non-matching rule. Moreover, because the Autism and Non-Autism groups were highly comparable in age and IQ, differences in performance were not due to differences in general cognitive ability or mental age. Difficulties in processing and discriminating faces and facial expressions but not objects have been associated with damage to a neural network involving the fusiform gyrus and the amygdala (Adolphs 2003; Schultz, Grelotti, Klin, Kleinman, Van der Gaag, Marois, & Skudlarski, 2003; Schultz, 2005) and the orbital frontal cortex (Rolls, 2007). Developmental dysfunction in these areas could also result in poorer discrimination of social-emotional stimuli, as was found in this study. Thus, the performance of the Autism group suggests dysfunction of the temporal cortex-amygdala-orbital frontal cortex circuit (see Winston, Strange, O'Doherty, & Dolan, 2002; Schultz 2005; Sasson, 2006).

The difficulty of persons with autism in the facial identity and facial expression conditions is consistent with recent reports in the literature (see for review Adolphs, Sears, & Piven, 2001; Grelotti et al., 2002; Gross, 2004; Howard et al., 2000; Lindner & Rosen, 2006; Pelphrey, Adolphs, & Morris, 2004; Sasson, 2006; Williams, Goldstein, & Minshew, 2005). In addition, scalp ERP recordings have revealed anomalies in temporal processing of faces in autism (Dawson et al., 2002; Dawson, Webb, Carver, Panagiotides, & McPartland, 2004; Dawson, Webb, & McPartland, 2005; McPartland, Dawson, Webb, Panagiotides, & Carver, 2004). Neuroimaging studies have also demonstrated that face-processing deficits in autism are associated with changes in activation of the fusiform gyrus and the cortical face area (Pierce, Haist, Sedaghat, & Courchesne, 2004; Schultz, 2005), and hyperactivation of the amygdala and orbital frontal cortex (Dalton et al., 2005). Given growing evidence implicating the amygdala and orbital frontal cortex in processing the emotional content of social signals (see Bachevalier & Loveland, 2006), the performance of the Autism group on face identity and facial expression discrimination suggests a dysfunction of structures within this neural system.

Conclusion: Orbitofrontal-Amygdala Circuit Tasks

On both the discrimination of social stimuli (Delayed Non-Match-to-Sample-facial identity and facial expression conditions) and the learning of a reversal discrimination with objects (Object Discrimination Reversal tasks), the Autism and Non-Autism groups differed, but did so more strongly in individuals with higher VMA. In general, VMA was a better predictor of performance on these tasks in the Non-Autism than in the Autism group. One can conclude that for the orbitofrontal-amygdala tasks, having a higher verbal developmental level confers

less of an advantage to individuals with autism than to those without autism. By contrast, lower VMA was associated with poorer performance in both groups.

Tasks measuring functions of the Dorsolateral Prefrontal-Hippocampus Circuit

Spatial Working Memory—Results for the Spatial Delayed Alternation task were straightforward: performance was significantly poorer in the Autism group. Performance in both groups was significantly and positively related to VMA.

The finding of spatial working memory impairment in this task parallels earlier findings on a spatial delayed response task (Dawson et al., 1998; McEvoy et al., 1993) and on a spatial reversal task in persons with autism (Coldren & Halloran, 2003; McEvoy et al., 1993) as well as other spatial working memory tasks (Landa & Goldberg, 2005; Williams, Goldstein, Carpenter, & Minshew, 2005; Williams, Goldstein, & Minshew, 2006). However, no impairment in spatial working memory was found in another study (Griffith et al., 1999), and one report (Ozonoff & Strayer, 2001) showed normal performance by higher IQ persons with autism on three different tasks of spatial working memory. Koshino et al. (2005) also demonstrated normal performance of higher IQ persons with autism on an "n-back task" measuring working memory, although brain activations in these individuals differed from those of controls. Since both animal lesion studies and human neuroimaging have shown that Spatial Delayed Alternation tasks tap preferentially into functioning of the dorsolateral prefrontal cortex (see for review Goldman-Rakic, 1988), the present findings as well as findings from earlier studies suggest that impaired functioning of the dorsolateral prefrontal region may be related to intellectual ability in individuals with and without autism. It is also interesting that severe deficits in spatial working memory have been reported in monkeys that received damage to dorsolateral prefrontal cortex in infancy (Goldman-Rakic et al., 1983). Impairment in spatial working memory emerged only when the animals reached adolescence, suggesting that age of the participants at testing should be taken into consideration and may be the reason for the conflicting results observed across studies.

Memory Span Tasks—The Autism group did not differ from the Non-Autism group in the Object Span control task, indicating relatively normal object recognition memory in the participants with autism, a finding congruent with their normal performance earlier in the Object Identity condition of the Delayed Non-Match-to-Sample task. However, on the Spatial Span task, mean span score was greater (better) in the Non-Autism group than in the Autism group, even when the effect of the Object Span control task was controlled. This finding is consistent with a recent study (Minshew & Goldstein, 2001) showing poorer performance of individuals with autism as compared to controls on spatial memory tasks, namely maze learning and spatial span. Other studies found normal, or near normal performance, in recognition and free recall tasks (Minshew & Goldstein, 1993), but impaired performance on tasks measuring episodic (relational) memory (Klein et al., 1999; Millward et al., 2000; Bowler et al., 2000; Ben Shalom, 2003). Given the critical role of the hippocampus in episodic and relational memory tasks, but not in item-specific memory tasks (Holdstock, Mayes, Roberts, Cezayirli, Isaac, O'Reilly, & Norman, 2002; Eichenbaum, Yonelinas, & Ranganath, 2007), the data imply a dysfunction of a system involving the hippocampus in persons with autism (Ben Shalom, 2003; Boucher et al., 2005).

Conclusions: Dorsolateral Prefrontal-Hippocampus Circuit Tasks—In both the Spatial Delayed Alternation and the Spatial Memory Span task large differences in performance were present between comparable individuals with and without autism at all levels of VMA. Thus, unexpectedly, spatial memory tasks thought to be subserved by the dorsolateral prefrontal-hippocampus circuit proved to be highly sensitive to autism diagnosis. Because the impairment was apparent for both the spatial recognition task (Spatial Memory Span) and the

spatial working memory task (Spatial Delayed Alternation), our results do not support the view that the spatial working memory deficit in autism is related to a computational difficulty imposed by the working memory task in the absence of environmental cues (Williams et al., 2005). Rather, the difficulty in the spatial memory tasks may have resulted from a more general difficulty in processing visuo-spatial information provided by the parahippocampal cortex and parietal lobe to the hippocampus and dorsolateral prefrontal cortex, respectively. Although evidence exists for involvement of the dorsal visual pathway in autism (Spencer, O'Brien, Riggs, Atkinson & Wattam-Bell, 2000; Pellicano, Gibson, Mayberry, Durkin, & Badcock, 2005; Bertone, Mottron, Jelenic & Faubert, 2005), further studies will be needed to characterize the neural process that results in spatial memory impairment. Moreover, recent findings (see for review Petrides, 2005) indicate that lateral prefrontal cortex may not support spatial working memory per se but rather the monitoring and manipulation of stimuli or events held in working memory in more posterior association cortex (e.g. parietal cortex and parahippocampal cortex). This possibility suggests that additional measures of executive functions in autism will be necessary using the behavioral tasks recently developed to tax cognitive processes mediated by lateral prefrontal cortex in both humans and monkeys.

General Conclusions

The hypotheses of this study hypotheses were of interest not only because they predicted relationships between specific brain circuits and autism, but also because they addressed a possible neuropsychological basis for both the socio-emotional deficits and the wide range of intellectual abilities observed among persons with autism. We found as predicted by Hypothesis 1 that impairment on tasks tapping the orbitofrontal-amygdala circuit was associated with autism diagnosis, but we also found that this association was stronger for more developmentally advanced individuals with autism (i.e., with higher VMA). Although in a cross-sectional study such as this one we cannot definitively identify developmental trends for the individual, differences in the functioning of the orbitofrontal-amygdala circuit associated with autism may increase along with the brain development of the child. Because the orbital frontal cortex and related ventral areas of the frontal cortex develop gradually and become fully functional in adolescence or even later (Hooper, Luciana, Conklin, Yarger, 2004; and see for review Segalowitz and Davies, 2004), a possible reason for this divergence over development could be the emerging effects of abnormalities in these structures and their effects on other structures to which they are linked. The lack of a difference in performance between participants of lower VMA with and without autism, and the generally poor performance of these individuals on the orbitofrontal-amygdala tasks, is consistent with some earlier research suggesting that developmentally young children with autism do not differ from peers without autism on tasks tapping this circuit. Dawson, Munson, Estes, Osterling, McPartland, Toth, et al. (2002) reported that 3 to 4 year olds with autism did not differ from young children with developmental delays or no disabilities in performance on tasks tapping the ventromedial prefrontal cortex. Like the children in Dawson's study with and without developmental disabilities, both younger and lower IQ participants in our study may not have attained a sufficient level of brain development to successfully perform tasks tapping this region of the brain. This idea is also consistent with recent findings indicating that when tested on the Object Discrimination Reversal task during infancy, control monkeys and those with neonatal orbital frontal lesions were equally impaired relative to adult monkeys (Kazama and Bachevalier, 2002), suggesting that both groups showed immaturity in the structures mediating performance on this task. In the case of the older children and adolescents with lower VMAs in our study, this finding implies that development of the ventral orbitofrontal-amygdala brain circuit may be slower than that of age peers (cf Shaw, Greenstein, Lerch, Clasen, Lenroot, Gogtay, et al., 2006; Zilbovicius, et al., 1995). However, other, perhaps simpler, tasks tapping the orbitofrontal-amygdala brain circuit (such as an extinction task) might be more sensitive to

differences in brain function between persons of lower developmental level who do and do not have autism.

Hypothesis 2 predicted that performance on tasks tapping the dorsolateral prefrontal-hippocampus circuit would be associated primarily with developmental level rather than autism diagnosis. Contrary to expectation, children and adolescents with autism had significant impairment on these tasks relative to the Non-Autism group across the full range of developmental levels represented. Interestingly, performance by Non-Autism group participants with lower VMAs equaled or exceeded that of more intellectually advanced individuals with autism. Ozonoff, Cook, Coon, Dawson, Joseph, Klin, et al (2004) in a study using prefrontal tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) also found differences between individuals with and without autism over a range of ages and IQs. Similarly, Williams, Goldstein, Carpenter, & Minshew (2005) and Landa & Goldberg (2005) found spatial working memory deficits in high-functioning persons with autism, at different ages. Given that the dorsolateral prefrontal cortex is a late developing structure, one might expect that this circuit, like the orbitofrontal-amygdala circuit to which it is closely linked, would gradually manifest abnormalities as the brain develops and the circuit becomes fully functional. However, results of this study suggest that performance on the dorsolateral prefrontal-hippocampus circuit tasks did not worsen with age in autism as compared to control individuals, as was suggested by some previous studies (Dawson et al., 2002; Griffith et al., 1999). Some possible reasons for these findings can be suggested. The tasks we used to measure hippocampus and dorsolateral prefrontal cortex functioning also required more fundamental processes involved in visual-spatial processing; these processes may be affected in autism (Bertone et al., 2005; Kemner & Van Engeland, 2006), which could lead to deficits in both the Spatial Memory Span and Spatial Delayed Alternation tasks. Impairment in these tasks across the full range of developmental levels in the Autism group may indicate that difficulty in more basic processes, such as the representation of visual-spatial information, affected spatial memory abilities in general. Such processes are known to be present in the first years of life in children and may reflect early development of posterior association cortex areas (Braddick, Atkinson, & Wattam-Bell, 2003; Parrish, Giaschi, Boden & Dougherty, 2005). Thus, dysfunction in these cortical areas in autism could result in cognitive difficulty that emerges early and remains throughout the individual's life.

Because the cognitive functions mediated by the dorsolateral prefrontal cortex and hippocampus in this study were restricted to the spatial memory domains, further studies are needed to investigate more fully the involvement of these brain regions in autism. For instance, future studies might include behavioral tasks taxing episodic memory functions (associated with hippocampal functioning), and tasks involving monitoring and manipulation of information in working memory (associated with the lateral prefrontal cortex). In conclusion, while the present findings support dysfunction of a circuit linking the amygdala and orbital frontal cortex in individuals with autism, additional studies are clearly required to demonstrate whether the circuit linking the hippocampus and dorsolateral prefrontal is equally affected in all individuals with autism irrespective of intellectual levels.

Acknowledgments

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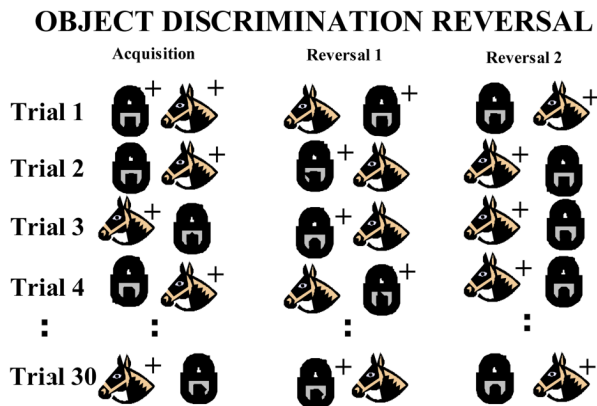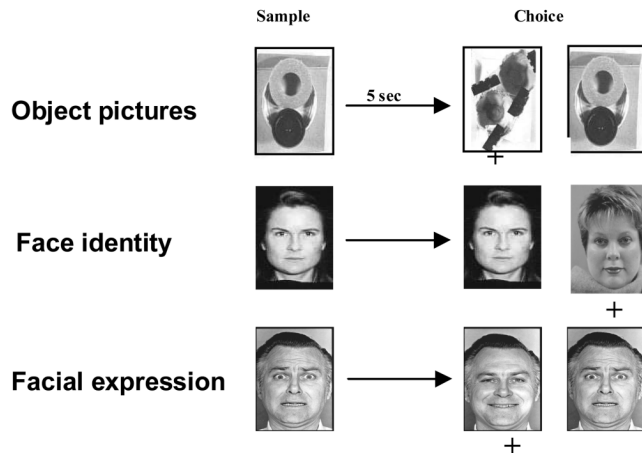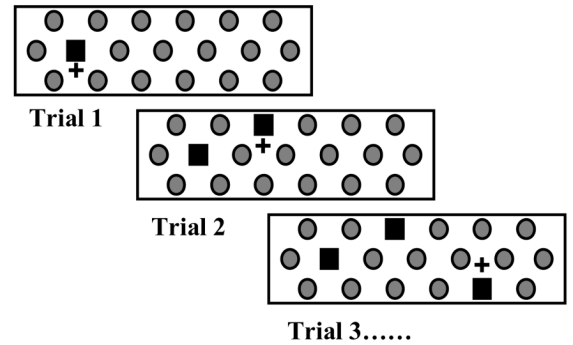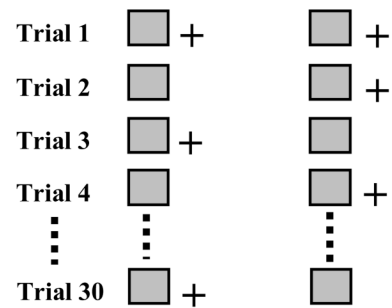
Figure 1.
Neuropsychological Tasks Given to Test Integrity of the Orbitofrontal-Amygdala Circuit and the Dorsolateral Prefrontal-Hippocampus Circuit.

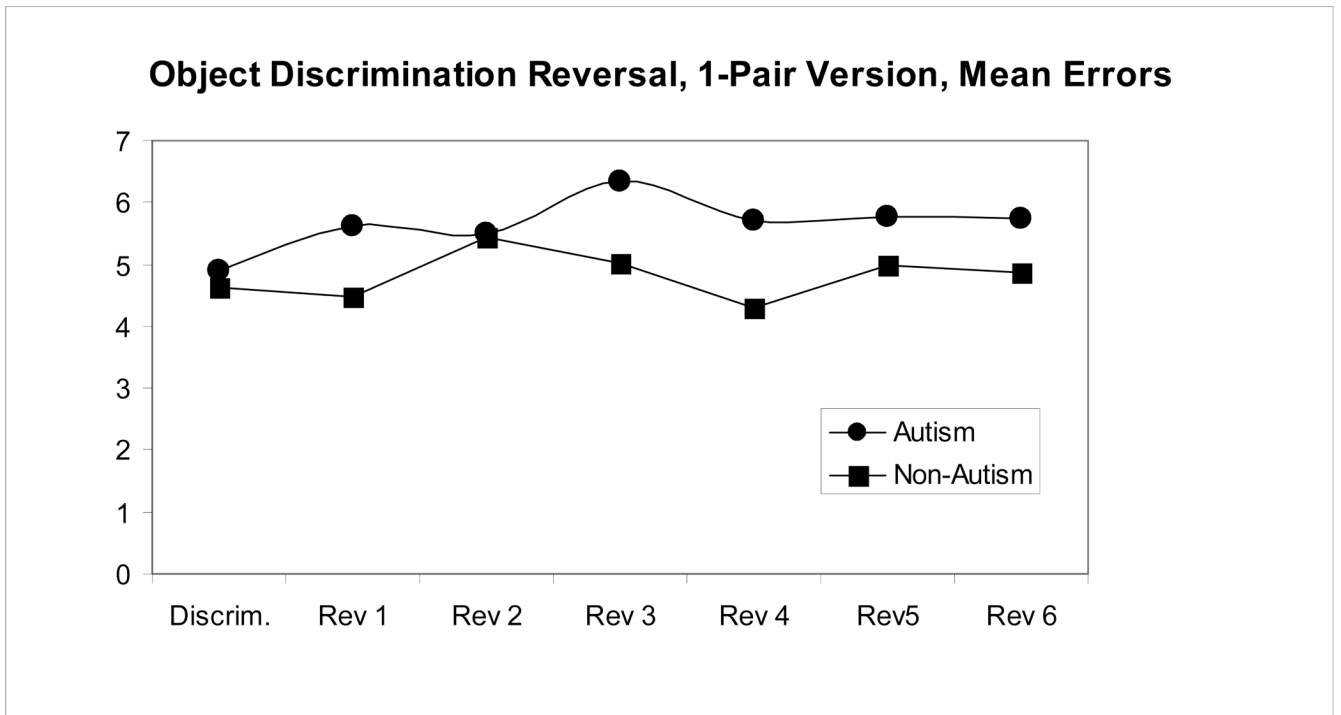## Object Discrimination Reversal, 1-Pair Version, Mean Errors

Figure 2.
Mean errors to criterion for the first discrimination and the subsequent 6 reversals of the Object Discrimination Reversal tasks for the Non-Autism and Autism groups.
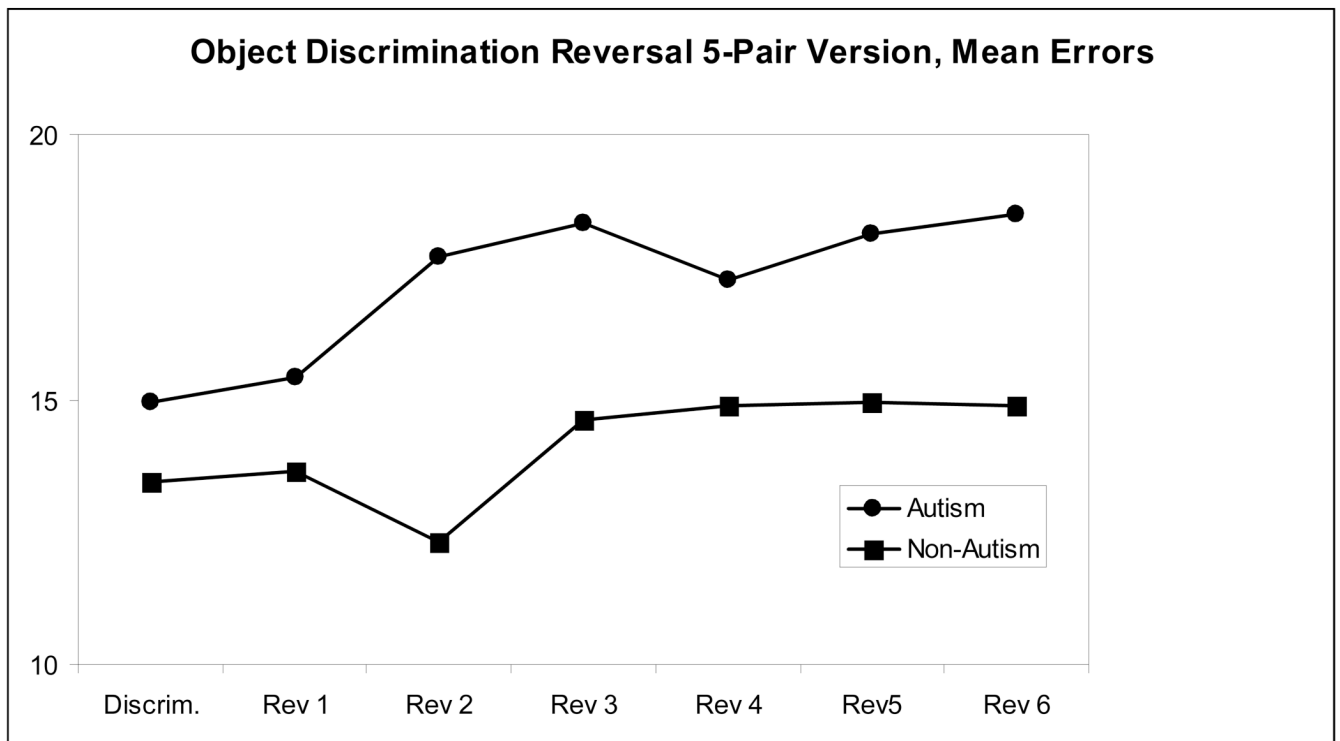
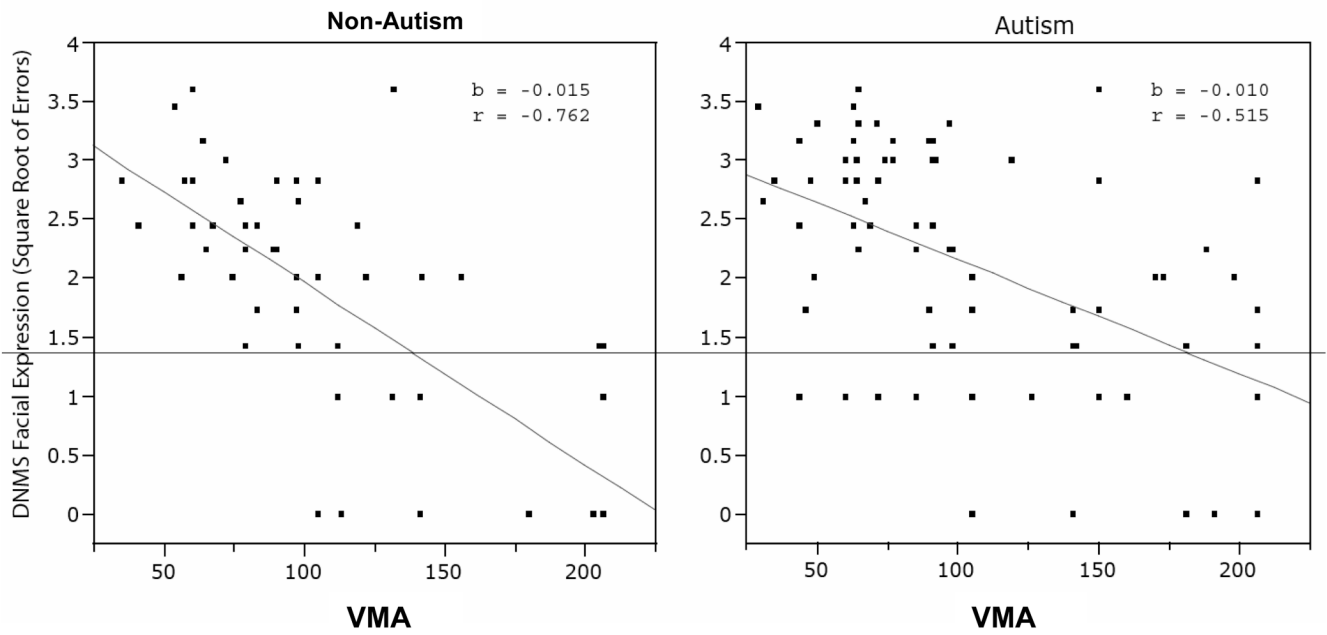## Object Discrimination Reversal 5-Pair Version, Mean Errors

Figure 3.
Mean errors to criterion for the first discrimination and the subsequent 6 reversals of the 5-pair
Object Discrimination Reversal task in the Non-Autism and Autism groups.

Figure 4.
Scores are square root of errors for each participant in the Non-Autism and Autism group as a function of VMA level.
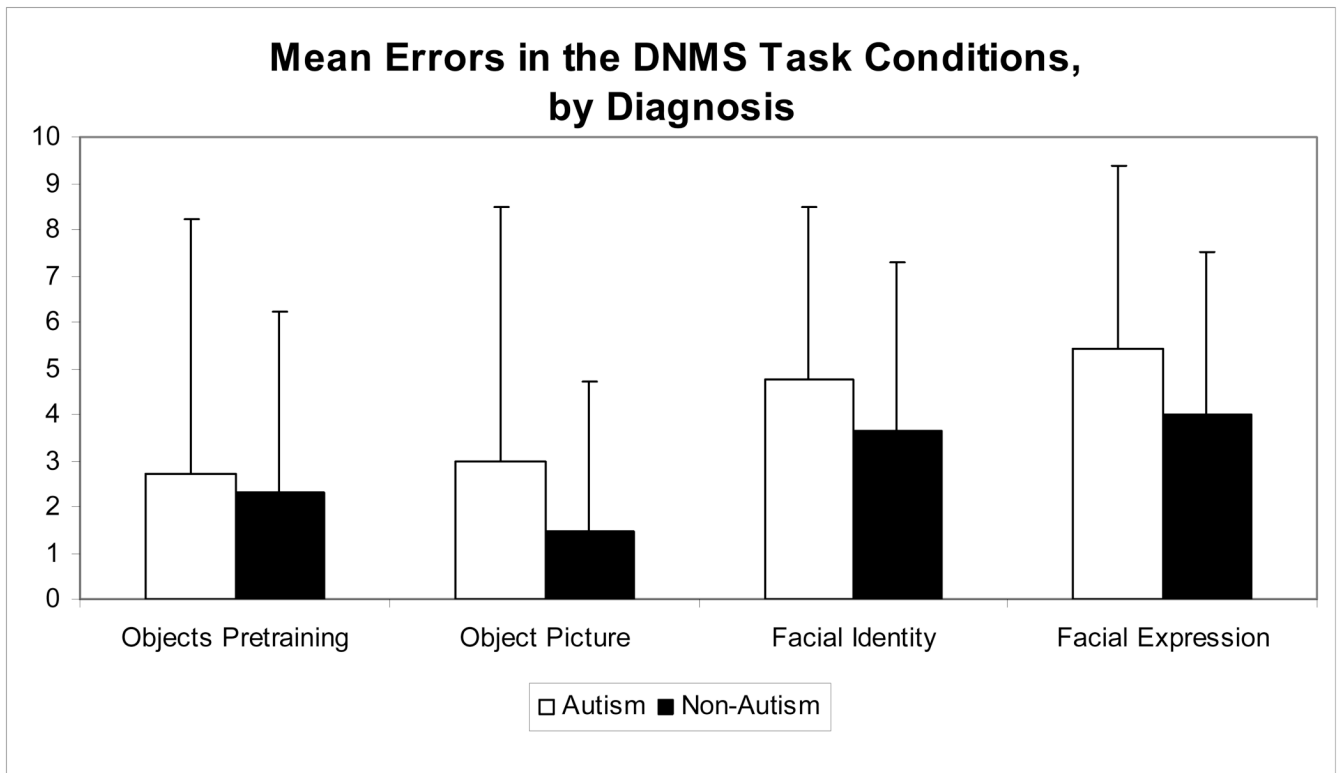
Figure 5.
Mean errors to criterion for the pre-training phase using 3-D objects and in the Object Pictures,
Facial Identity and Facial Expression conditions for the Non-Autism and Autism groups.
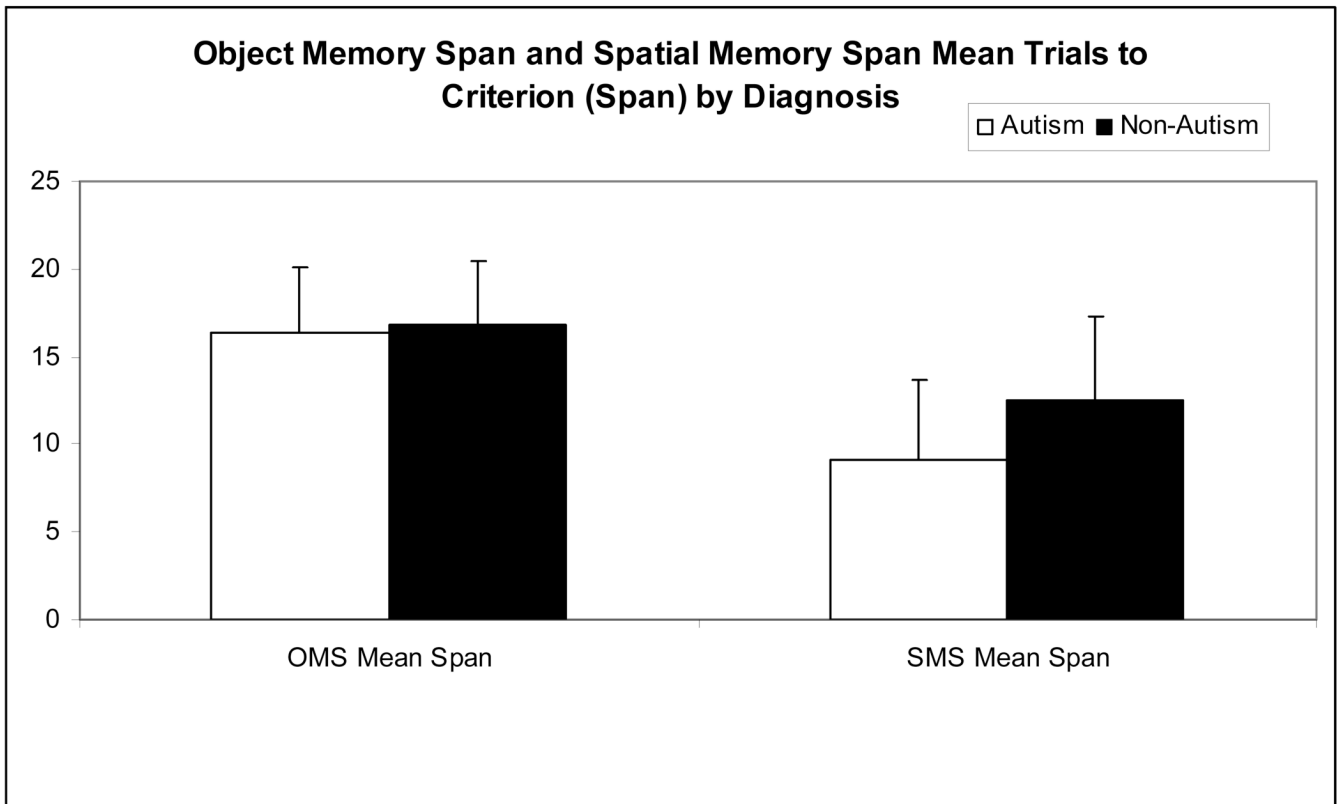
Figure 6.
Mean Span Scores for the Object Memory Span and the Spatial Memory Span tasks for Non-autism and Autism groups.
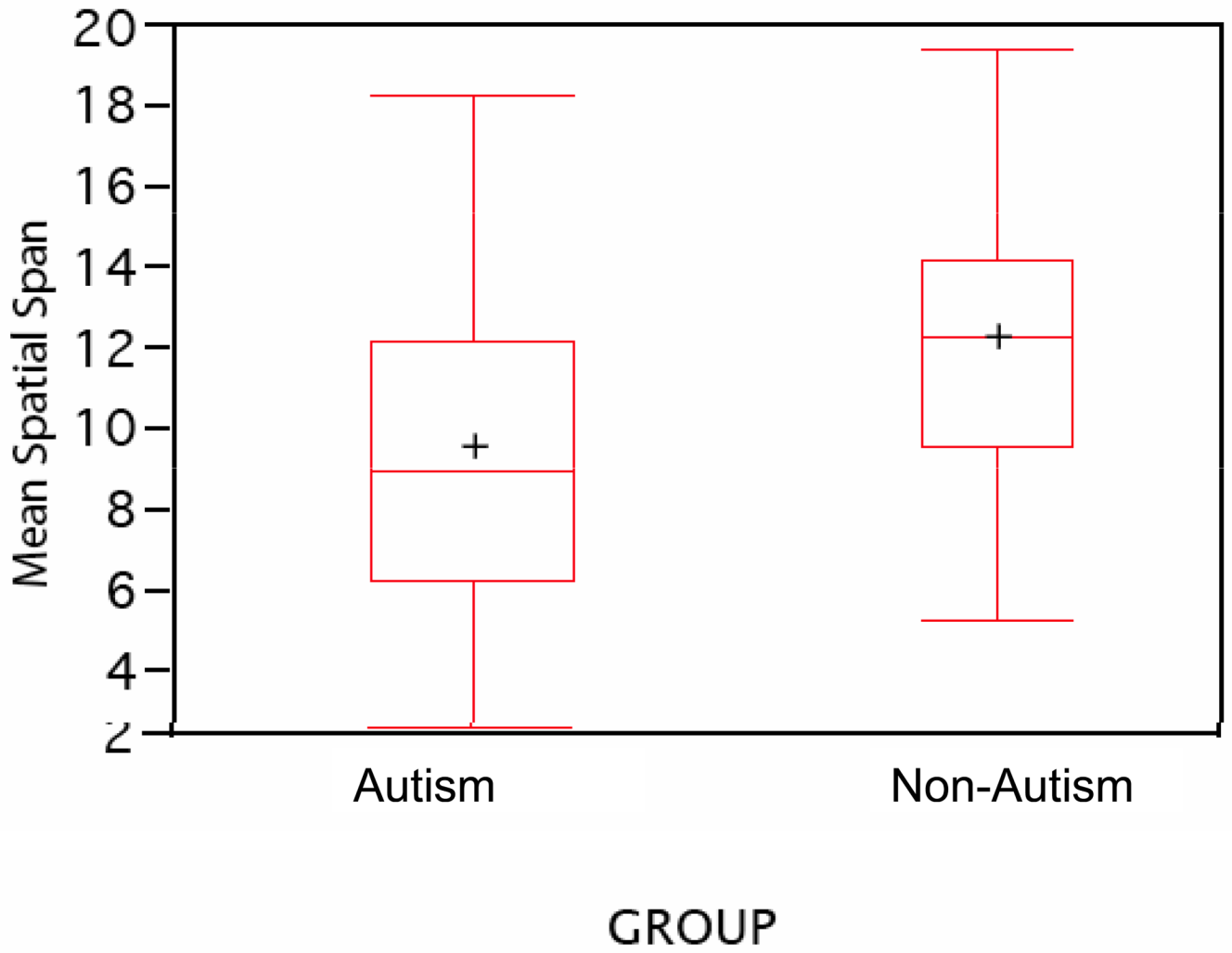
Figure 7.
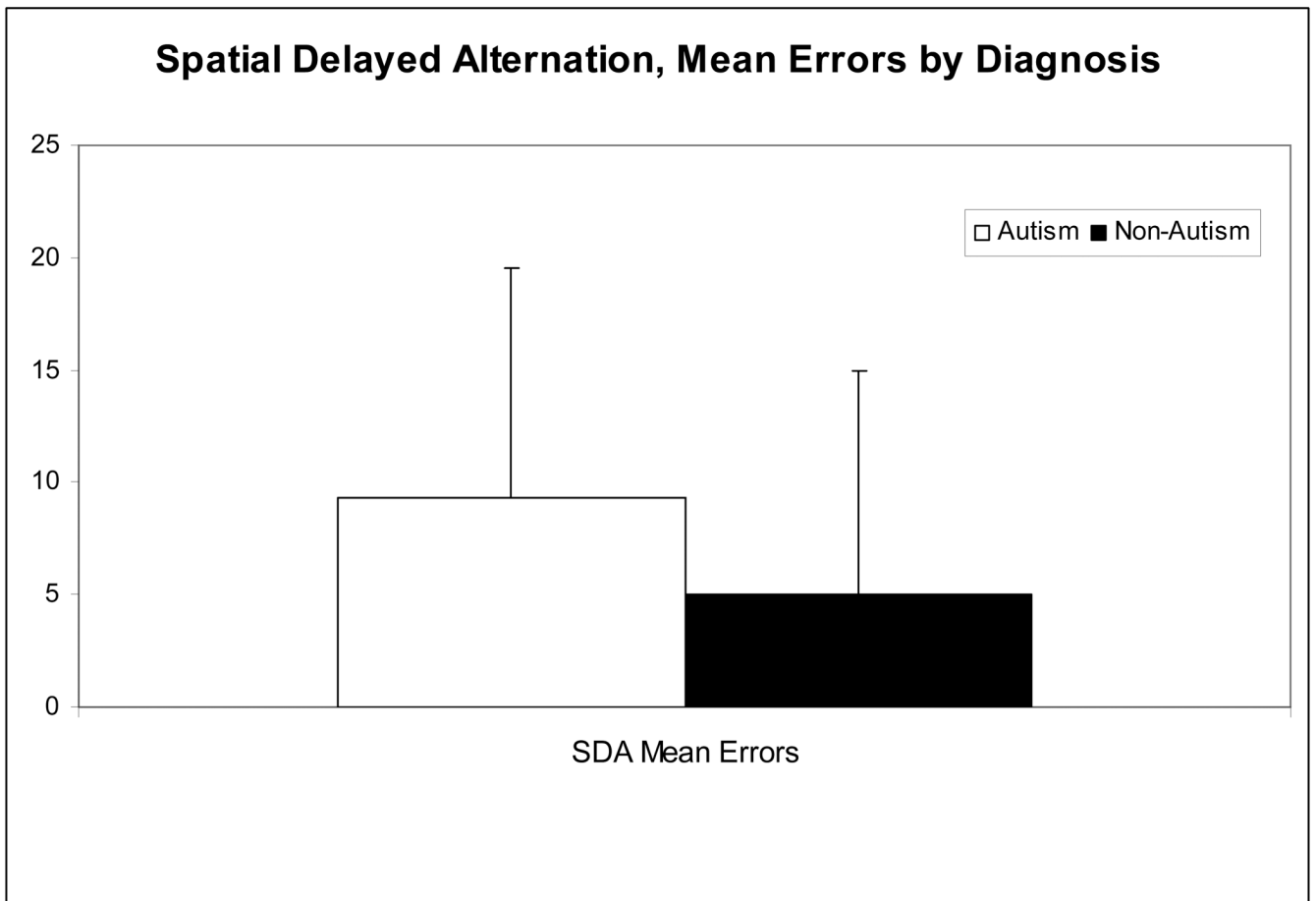Mean Spatial Memory Span scores by Group.

Figure 8.
Mean errors to criterion in the Spatial Delayed Alternation task in the Non-Autism and Autism groups.

Table 1

Participant characteristics

VIQ = Stanford-Binet 4, Verbal Reasoning SAS; NVIQ = Stanford-Binet 4, Abstract-Visual Reasoning SAS. CA = chronological age. Note that all participants received the One-Pair Object Discrimination Reversal (ODR). A subset of participants also received the Five-Pair version of the ODR.

		Full Sample Receiving One-Pair ODR Autism, n = 80 Non-Autism, n = 58			**Sub-Sample Receiving Five-Pair ODR Autism, n = 44 Non-Autism, n = 37**		
	Group	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
CA (Months)	Autism	143.8	37.2	85–225	150.6	35.7	87–224
	Non-Autism	149.3	38.8	84–224	148.0	37.9	84–209
VIQ	Autism	80.7	26.7	36–154	89.1	27.4	39–154
	Non-Autism	87.3	26.6	40–142	96.3	25.9	54–142
NVIQ	Autism	88.1	26.0	36–154	97.3	25.5	51–154
	Non-Autism	90.9	26.5	41–138	98.4	22.7	49–138