HHS Public Access

Author manuscript

Neuroimage. Author manuscript; available in PMC 2017 January 15.

Published in final edited form as:

Neuroimage. 2016 January 15; 125: 332–341. doi:10.1016/j.neuroimage.2015.10.039.

Diminished Neural Adaptation during Implicit Learning in Autism

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Abstract

Neuroimaging studies have shown evidence of disrupted neural adaptation during learning in individuals with autism spectrum disorder (ASD) in several types of tasks, potentially stemming from frontal-posterior cortical underconnectivity (Schipul *et al.*, 2012). The aim of the current study was to examine neural adaptations in an implicit learning task that entails participation of frontal and posterior regions. Sixteen high-functioning adults with ASD and sixteen neurotypical control participants were trained on and performed an implicit dot pattern prototype learning task in a functional magnetic resonance imaging (fMRI) session. During the preliminary exposure to the type of implicit prototype learning task later to be used in the scanner, the ASD participants took longer than the neurotypical group to learn the task, demonstrating altered implicit learning in ASD. After equating task structure learning, the two groups' brain activation differed during their learning of a new prototype in the subsequent scanning session. The main findings indicated that neural adaptations in a distributed task network were reduced in the ASD group, relative to the neurotypical group, and were related to ASD symptom severity. Functional connectivity was reduced and did not change as much during learning for the ASD group, and was related to ASD symptom severity. These findings suggest that individuals with ASD show altered neural adaptations during learning, as seen in both activation and functional connectivity measures. This finding suggests why many real-world implicit learning situations may pose special challenges for ASD.

Keywords

autism spectrum disorder; functional magnetic resonance imaging; functional connectivity; implicit learning; prototype

Introduction[1]

Numerous studies have identified atypical neural processes underlying cognitive task performance in autism spectrum disorder (ASD), yet few have examined the neural

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[1]**Abbreviations:** ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; MNI = Montreal Neurological Institute; NT = neurotypical individuals; ROI = region of interest

mechanisms that function while learning is occurring. Evidence of atypical patterns of brain activation during cognitive task performance in ASD, even in cases where individuals with ASD do not show a behavioral disadvantage, suggest that there may be something qualitatively different in the way individuals with ASD perform such tasks. It is possible that these neural differences arise because individuals with ASD learn in atypical ways (that may or may not be reflected in behavioral performance). Therefore, brain imaging studies of the learning process in ASD may reveal insights into the disorder that are not discernible from behavior alone. The present study aimed to examine neural adaptations in ASD during implicit learning with the goal of identifying neural disruptions in the disorder that may affect behavior in many real-world situations.

There is increasing evidence that brain function consists of networks of regions operating collaboratively, and that communication among brain regions may be disrupted in ASD. One theory posits that brain communication in ASD is impaired particularly between frontal and posterior regions (Just *et al.*, 2004, 2012), based on widespread evidence of reduced anatomical and functional (synchronization) connectivity in ASD (for a review, see Schipul *et al.*, 2011). Because learning typically relies on the integration of a large network of regions throughout the brain, it may be particularly susceptible to disorders of connectivity. Limited communication between distinct brain regions in ASD may impair coordination among these regions during the learning of a novel task, as well as the ability to streamline neural processes necessary to perform the task. In this way, brain underconnectivity may lead to impaired learning in ASD, particularly for learning processes that depend on the integration of a widely distributed task network.

Implicit learning is a type of learning that may be particularly affected and informative to study in ASD. Implicit learning refers to the acquisition of information about the world that arises without an intention to learn or without conscious access to what we know (Perruchet and Pacton, 2006; Reber, 1989), and includes tasks ranging from motor sequence memorization to visual pattern abstraction. Implicit learning is believed to underlie the learning of behaviors in two domains that are diagnostically disrupted in ASD, social interaction and language (Gomez and Gerken, 1999; Lieberman, 2000; Saffran *et al.*, 1997), which may implicate implicit learning in the emergence of core symptoms of ASD. Previous behavioral work has provided mixed evidence of implicit learning abilities in ASD, suggesting possible impairments, discussed below. Finally, because many types of implicit learning rely on distributed cortical networks, they may be impacted by disruptions in brain connectivity. The present study utilized a non-social, non-verbal visuospatial task to isolate neural and behavioral patterns of basic implicit learning in ASD, which should be minimally affected by deficits in social interaction and language. The study investigated the disruption in neural learning mechanisms in autism by examining neural adaptations with a focus on functional connectivity during an implicit learning task.

1.1 Implicit Learning in ASD

Previous behavioral studies of implicit learning in children and adults with ASD have revealed a mixed pattern of results across different types of tasks. Motor sequence reaction time tasks report both intact (Barnes *et al.*, 2008; Brown *et al.*, 2010; Gordon and Stark,

2007; Müller *et al.*, 2004; Nemeth *et al.*, 2010; Travers *et al.*, 2010) and impaired (Gidley Larson and Mostofsky, 2008; Mostofsky *et al.*, 2000) performance. Mixed results have also been reported in artificial grammar tasks (intact: Brown *et al.*, 2010; Klinger *et al.*, 2007; impaired: Klinger *et al.*, 2007) and probabilistic learning (intact: Brown *et al.*, 2010; Solomon *et al.*, 2011; impaired: Scott-Van Zeeland, *et al.*, 2010a). Previous studies reported intact behavior in contextual cueing (Brown *et al.*, 2010; Kourkoulou *et al.*, 2011), while a more recent study found intact performance when both spatial and object identity cues were available, but impaired performance when only object cues were provided (Travers *et al.*, 2013).

Visual prototype learning tasks require the participant to abstract a representation of a category based on exposure to multiple exemplars and these tasks have also shown mixed results in ASD. There is evidence of impaired prototype learning in ASD for face stimuli (Gastgeb *et al.*, 2009, 2011b) and cartoon animal stimuli (Klinger and Dawson, 2001; Klinger *et al.*, 2007). However, others have reported a wide range of performance across ASD participants using similar stimuli (Molesworth *et al.*, 2008), suggesting that this is a fragile disruption in ASD. Dot pattern categories are particularly useful stimuli in prototype learning studies, because they can be precisely controlled and are comparably familiar across participant groups. Again, results have been mixed in ASD, with evidence of both intact (Froehlich *et al.*, 2012; Molesworth *et al.*, 2005) and impaired (Church *et al.*, 2010; Gastgeb, *et al.*, 2011a; Vladusich *et al.*, 2010) performance relative to neurotypical participants.

Several explanations of the mixed findings of implicit learning abilities in children and adults with ASD have been proposed, including that certain tasks may allow the use of explicit strategies whose execution is closely related to IQ (Klinger *et al.*, 2007; Brown *et al.*, 2010); that individuals with ASD may be able to learn from certain types of cues (e.g., spatial cues), but not others (e.g., object identity, Travers *et al.*, 2013); or that individuals with ASD can learn but may take longer to do so (Vladusich *et al.*, 2010). The present study aimed to reduce such potential confounds by selecting a task that cannot be performed explicitly, equating participant groups on IQ, using spatial stimuli, and training participants to a set learning criterion prior to the scanning session. Furthermore, neuroimaging may indicate disruptions in neural processing during implicit learning in ASD even when behavior appears intact, which may suggest underlying impairments that may affect behavior in more demanding conditions (e.g., increased task difficulty or a shorter learning session). Neuroimaging may also reveal whether implicit or explicit strategies are used as they give rise to activation in different brain regions (i.e. basal ganglia vs. medial temporal lobe, Poldrack *et al.*, 2001).

1.2 Neural Adaptations during Typical Learning

Typical patterns of activation change during learning have been identified in neurotypical individuals. The predominant adaptation during learning is a decrease in activation throughout the network of association areas involved in the task (for a review, see Kelly and Garavan, 2005), including areas responsible for control processes (Chein and Schneider, 2005). This effect is thought to reflect increased neural efficiency, because the same

behavioral performance is achieved with fewer mental resources. Decreases in activation over the course of learning have also been found in sensory processing areas, an effect known as repetition priming (Desimone, 1996). In contrast, activation increases during learning occur in medial temporal and subcortical areas involved in stimulus response mappings (Salimpoor *et al.*, 2010), and have been shown to correlate directly with behavioral performance improvements (Salimpoor *et al.*, 2010). Finally, the synchronization of fMRI-measured activation across different brain regions involved in a task has been shown to increase over the course of learning, resulting in increased functional or effective connectivity (Büchel *et al.*, 1999; Toni *et al.*, 2002). In summary, typical neural adaptations during learning include decreased association area activation, decreased sensory area activation, increased subcortical and medial temporal activation, and increased inter-region synchronization.

1.3 Neural Adaptations during Learning in ASD

Few fMRI studies have assessed the neural mechanisms of learning in ASD. The changes in activation patterns during the learning of a complex social task have been shown to be disrupted in ASD relative to neurotypical participants, despite similar behavioral improvements across groups (Schipul *et al.*, 2012). While neurotypical adults demonstrated decreases in activation in association and sensory processing regions and increases in medial temporal and subcortical regions, adults with ASD showed a more unchanging pattern of activation throughout learning, showing only small decreases in sensory processing areas and increases in task-related association areas. Neurotypical participants also showed larger increases in functional connectivity than did the ASD participants. These findings suggest that the neural processes in ASD participants did not adapt over the course of learning in the context of intact behavioral performance. It is unclear if this effect is specific to the social domain or generalizable to other types of learning in ASD.

While no other studies have focused on neural adaptation during learning in ASD, evidence can be found in existing related studies. Adults with ASD were shown to maintain activation in frontal premotor regions during motor sequence learning, while neurotypical adults generally showed decreases in these areas (Müller *et al.*, 2004). ASD adults were shown to have decreased activation in the fusiform gyrus, but not the amygdala, after extended exposure to faces, while neurotypical adults had decreases in both regions (Kleinhans *et al.*, 2009). Facial affect recognition training was associated with increased activation in parietal and occipital regions in adults with ASD (Bölte *et al.*, 2006). In an artificial language study, neurotypical children showed neural sensitivity to the systematicity of artificial language stimuli, as well as increasing activation with extended exposure, while children with ASD showed no distinguishing activity for artificial language compared to random stimuli, nor for extended exposure (Scott-Van Zeeland, *et al.*, 2010b). Studies have also shown evidence of atypical neural responses to rewards during learning in children and adults with ASD (Kohls *et al.*, 2012; Schmitz *et al.*, 2008; Scott-Van Zeeland, *et al.*, 2010a). Thus, preliminary evidence suggests that neural processes during learning are disrupted in ASD. However, further investigation is necessary to isolate these effects with regard to specific types of learning.

1.4 Aim of the Present Study

The aim of the present study was to examine the neural adaptations during implicit learning in ASD. We hypothesized that the ASD group would have disruptions in implicit learning due to effects of underconnectivity on a task requiring a distributed network. We examined changes in brain activation and synchronization occurring over a short-term learning task. The relations between ASD symptom severity and both neural adaptations and synchronization were assessed to test the hypothesis that ASD characteristics are directly related to disrupted neural mechanisms of learning. This study tested several hypotheses: (1) neural adaptations during implicit learning will be disrupted in ASD; (2) the ASD group will have lower synchronization that changes less over time than the neurotypical group; (3) ASD symptom severity will relate to both neural adaptations and synchronization; (4) ASD participants will show behavioral deficits in the implicit learning task.

To examine neural changes during implicit learning in ASD, we developed a dot pattern prototype paradigm. Participants were exposed to many unique dot patterns that belonged to a category based on their similarity to a prototype and were later tested on category membership of novel patterns. Prior to the scanning session, participants were familiarized with the task until they reached a behavioral performance criterion. During the scanning session, participants performed the task on a separate set of stimuli. Brain activation and synchronization were measured throughout the exposure blocks. Differences in behavior, brain activation, and synchronization were compared between groups and over the course of learning (from early to late blocks).

Materials and methods

2.1 Participants

Sixteen high-functioning (IQ≥80) individuals with ASD and sixteen neurotypical individuals (NT) were included in the analysis. Participants were matched (see Table 1) on age, full scale IQ, gender, race, and socioeconomic status (Hollingshead, 1957). ASD diagnosis was established using the ADI-R (Autism Diagnostic Interview-Revised, Lord *et al.*, 1994) and the ADOS (Autism Diagnostic Observation Schedule, Lord *et al.*, 2000), and confirmed by expert clinical judgment. ADOS testing was performed within 1.5 years of the scanning session for 13 of 16 participants, and within 2.6 years for the remaining 3. ASD participants were excluded if there was an identifiable cause, e.g. fragile-X syndrome. NT participants were community volunteers and were excluded if they had an immediate family member with ASD, disorders of development, affect, or anxiety, or other genetic neurologic or psychiatric disorders. NT participants were screened by questionnaire, telephone, face-to-face interview, and observation during initial testing, and were excluded if they had current or past psychiatric and neurologic disorders, developmental delay, learning disabilities, substance abuse, central nervous system disorders, or disorders requiring regular medication. NT and ASD participants were excluded if there was evidence of birth asphyxia, head injury, or a seizure disorder. IQ was assessed for all participants using the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999). All participants signed an informed consent approved by the University of Pittsburgh and Carnegie Mellon University Institutional Review Boards.

2.2 Materials and Procedure

Participants performed a category discrimination task on dot pattern prototype stimuli. The stimuli consisted of nine white dots on a black background. Each category set contained three types of category members (prototype, low distortions, and high distortions) and non-category members (foils). The prototype for each category was a random array of nine dots within the center 30×30 units of a 50×50 space. Distortions were based on the methods of Posner and Keele (1968) and Posner *et al.* (1967), created by adjusting the positions of some or all of the dots in the prototype, with the level of distortion determined by the number of dots adjusted and the degree of each adjustment, shown in Table 2. The Hungarian Method (Kuhn, 1955) estimated distances between dot patterns and confirmed that the prototype was more similar to low distortions (mean distance: 5.7) than to high distortions (mean distance: 22.6). Foils were high distortions of a distinct random dot pattern and were equally distinct from all category members (prototypes: 76.1; low distortions: 75.7; high distortions: 77.6). Two distinct category sets were created: one to be used in the familiarization session and one to be used in the scanning session (examples shown in Fig. 1).

The experiment consisted of Encoding and Test blocks. In Encoding blocks, participants saw high distortion category members on the screen above a category label (“A”; Fig. 2), as high distortions have been shown to lead to more complete category learning (Posner and Keele, 1968). Participants were instructed that they would “see many patterns in a row that belong to one group. Look at each pattern and try to learn what types of patterns belong in that group.” In each block, five dot patterns were presented for 5000ms each with a 500ms interstimulus interval (27s total).

In Test blocks, participants saw either a category member (~50%) or a foil (~50%) and indicated category membership by pressing a button with their left hand for category members (e.g., “A”) or with their right hand for foils (e.g., “Not A”). Labels for both choices appeared on the screen. Participants were instructed that they would “see a pattern and decide if it belongs to the group or not.” Participants could respond during the 400ms dot pattern presentation, which was followed by 2s feedback presented alongside the dot pattern. Feedback consisted of the label for the correct answer (e.g., “A”) alongside a green checkmark for correct or a red “X” for incorrect, as shown in Fig. 2. In each block, five items were presented (6s each) with a 500ms interstimulus interval (32s total).

Immediately prior to the scanning session, participants completed multiple training runs on one of the category sets (counterbalanced across participants) until they reached an accuracy criterion of 70%. Training run 1 consisted of eight Encoding and three Test blocks. Training runs 2 through 5 consisted of four Encoding and two Test blocks. All participants completed Training runs 1 and 2 and continued until they reached accuracy criterion, with no participants requiring more than four runs. All but one participant (NT) completed an additional training run during acclimation in a scanner simulator. During training, participants saw each category member 2–3 times and each foil only once.

The experimental session took place in the fMRI scanner and consisted of twelve Encoding and twelve Test blocks. The current analysis includes six Encoding and six Test blocks that used a category set (labeled “B”) that was distinct from the one used in the training session

in order to reflect early learning. An additional six Encoding and six Test blocks used the task familiarization category set, but are not included here. Block types were presented in pairs, with a 7s rest between blocks. 24s fixations were presented before each pair of Encoding blocks (6 total). Table 3 presents the order of conditions. Across the 6 Test blocks, there were sixteen category members and fourteen non-category members (54% category responses), including one prototype, five unseen low distortions, five unseen high distortions, and five high distortions that were seen during earlier Encoding blocks.

The two category sets were counterbalanced across participants, such that half saw category 1 during familiarization and category 2 only in the scanning session. In the scanning session, category set had a main effect on error rate ($F(1,28)=4.42$, $p=0.04$), but not on reaction time ($F=2.3$). However, there was no interaction between Category set and Group or Time for either behavioral measure ($F<2$), so this variable was collapsed over for the remaining analyses.

2.3 Neuroimaging Acquisition

Data were collected using a 3T Siemens Verio Scanner and 32-channel phased-array head coil (Siemens Medical Solutions, Erlangen, Germany) at the Scientific Imaging & Brain Research Center of Carnegie Mellon University. The fMRI data were acquired with a gradient echo, EPI sequence with TR = 1000 ms, TE = 25 ms, a 60° flip angle, using GRAPPA parallel imaging and an iPAT factor of two. Twenty AC/PC-aligned oblique-axial slices were acquired in an interleaved sequence; each slice was 5 mm thick with a gap of 1 mm between slices. The acquisition matrix was 64×64 with 3.125×3.125×5-mm voxels.

2.4 Behavioral Analyses

Error rates and reaction times recorded by the experimental software for the Test blocks were submitted to 2 (Group) × 3 (Time: Early, Middle, and Late blocks) ANOVAs.

2.5 fMRI Analyses – Distribution of Activation

The distribution of activation was analyzed and compared using both one-sample t-tests (within group effects) and two-sample t-tests (between group effects) in SPM8. Images were corrected for slice acquisition timing, motion-corrected, normalized to the Montreal Neurological Institute (MNI) template, resampled to 2 × 2 × 2-mm voxels, and smoothed with an 8-mm Gaussian kernel to decrease spatial noise. Statistical analysis was performed on individual and group data using the general linear model and Gaussian random field theory as implemented in SPM2 (Friston *et al.*, 1995). Group analyses were performed using a random-effects model. Statistical maps were superimposed on normalized T1-weighted images. An uncorrected height threshold of $p<.005$ and an extent threshold of ten voxels were used.

Brain activation was analyzed only for Encoding to isolate the learning process. Activation was computed as the contrast between all Encoding blocks with Fixation. Activation changes over time were computed as the contrast between Early Encoding blocks (1–2) and Late Encoding blocks (5–6). To measure the relation between ASD severity and activation

changes over time, a simple regression was performed in SPM on the contrast between Early and Late Encoding blocks, with ADOS Total Score entered as a covariate.

2.6 fMRI Analyses – Functional Connectivity

Functional connectivity was computed separately for each participant as a correlation between the average time course of signal intensity of the thirty most activated voxels (to equate the number of voxels across regions) in each member of a pair of regions of interest (ROIs). Fisher's *r* to *z* transformation was applied to the correlation coefficients for each participant to ensure normality of the distributions prior to averaging and statistical comparison of the groups. Thirty-three functional ROIs were defined to encompass the main clusters of activation in the group activation maps in the Encoding-Fixation and Test-Fixation contrasts. Although the ROIs were defined on both Encoding and Test blocks to encompass all active regions in this task, the analysis was limited to the activation and synchronization during only the Encoding blocks because the focus of the research was on the implicit learning during encoding. Labels were assigned with reference to the automated anatomical labeling atlas (Tzourio-Mazoyer *et al.*, 2002): right anterior middle frontal gyrus, right middle frontal gyrus, right anterior inferior frontal gyrus, right caudate, right thalamus, right fusiform gyrus, left superior frontal gyrus, left inferior frontal gyrus, left cerebellum, supplementary motor area, posterior cingulate, and eleven bilateral ROIs: orbital middle frontal gyrus, precentral gyrus, insula, superior parietal lobule, inferior parietal lobule, inferior temporal gyrus, middle occipital gyrus, inferior occipital gyrus, calcarine fissure, lingual gyrus, and medial cerebellum. For each ROI a sphere (radii ranging from 4 to 10 mm) was defined to capture the activation in the Test-Fixation contrast separately for each group. ROIs with low activation in Test-Fixation were defined on Encoding-Fixation. Each sphere centered on the local maxima of an activation cluster. The ROIs used in the analysis were each the union of the two spheres defined for the two groups. The activation time course originated from the normalized and smoothed images, which were high-pass filtered and had linear trends removed. Participants with fewer than eight activated voxels in a given ROI were excluded from further functional connectivity analyses involving that ROI to ensure that correlations were based on stable estimates of the time course of the signal (on average < 4% ROI pairs and < 1 network pair per participant). To ensure the group comparison was not affected by differential amounts of head motion (Power *et al.*, 2012; Satterthwaite *et al.*, 2013), motion metrics based on changes from one volume to the next were computed, including the framewise displacement and the derivative of the root mean square variance in signal over voxels (see Power *et al.*, 2012 for details on these measures). No group differences in the mean, range, or variance of these measures approached significance. Thus, any group differences in functional connectivity that might emerge are extremely unlikely to have been affected by differential head motion.

Functional connectivity was measured for each participant separately for Early (1–2), Middle (3–4), and Late (5–6) Encoding blocks. The thirty-three ROIs were grouped on the basis of location (frontal, parietal, temporal, occipital, subcortical, or cerebellum) and functional connectivity measures for these groups of ROIs were obtained for each participant by averaging the connectivities of all relevant ROI pairs. This resulted in twenty-one "network pairs" for which connectivities were aggregated, including fifteen inter-lobe

pairs and six intra-lobe pairs. Functional connectivity measures were analyzed separately for frontal:posterior pairs (frontal:parietal, frontal:temporal, frontal:occipital) and non-frontal:posterior pairs (remaining 18 network pairs), following previous findings of frontal-posterior underconnectivity in ASD. The network pair connectivities were submitted to two distinct 2 (Group) × 3 (Time: Early, Middle, Late) mixed ANOVAs, with network pairs as repeated measures (one ANOVA for the 3 frontal:posterior pairs and a second ANOVA for the 18 non-frontal:posterior pairs). To measure the relation between ASD severity and functional connectivity, correlations were calculated between ADOS Total, Social, and Communication scores and functional connectivity measures.

2.7 fMRI Analyses – Percent Signal Change

Percent signal change analyses were conducted to examine a priori hypotheses concerning activation decreases over time, based on previous findings (Schipul *et al.*, 2012). This measure was computed for each participant as the mean percentage increase in signal relative to the fixation condition (averaged over the thirty most activated voxels in an anatomically-defined ROI) during the Encoding blocks. The signal measure was based on normalized and smoothed images, which were high-pass filtered and had the linear trend removed. Five bilateral anatomical regions of interest were chosen based on the previous findings of decreasing activation over time in NT but not ASD participants (Schipul *et al.*, 2012): middle frontal gyrus, precentral gyrus, postcentral gyrus, inferior temporal gyrus, and inferior parietal sulcus, as these regions are defined by the automated anatomical labeling atlas (Tzourio-Mazoyer *et al.*, 2002). The ROI percent signal change values were submitted to a 2 (Group) × 3 (Time: Early, Middle, Late) mixed ANOVA, with ROIs as repeated measures.

Results

3.1 Group Differences in Brain Activation

Although the brain activation of the two groups occurred in similar *locations* during the encoding blocks, the groups differed markedly in the *degree of adaptation over time*. Both groups showed activation throughout a large network of areas involved in visual processing (bilateral superior, middle and inferior occipital gyri), spatial processing (superior and inferior parietal lobules), executive functioning (bilateral superior and middle frontal gyri, right inferior frontal gyrus), and motor planning (bilateral precentral gyrus), as shown in Fig. 3 and Inline Supplementary Table 1. Two-sample t-tests revealed that the ASD group recruited somewhat larger clusters of activation in some of these areas, as well as additional clusters in bilateral supplementary motor area and middle cingulate (Inline Supplementary Table 1). Activation maps separated by Early, Middle, and Late blocks can be seen in Inline Supplementary Figure 1. These findings demonstrate that ASD and NT participants activated similar brain regions during implicit encoding.

3.1.1 Adaptations over time—Group activation differences were found in the amount of activation change over the course of the learning process, such that the participants with ASD showed an absence of activation decreases over time (as shown in the left-hand panels of Fig. 4), accompanied by activation *increases* over time (right-hand panels of Fig. 4),

whereas the NT participants showed *large reductions* in activation in several areas (left-hand panels of Fig. 4). The ASD group showed increased activation in Late blocks in most of the task network, including areas involved in executive functioning (bilateral anterior and middle cingulate, bilateral superior and middle frontal gyri, right inferior frontal gyrus), motor planning (right precentral gyrus), word and pattern recognition (right supramarginal gyrus, bilateral middle and superior temporal gyri), and implicit learning (left putamen), as well as left olfactory sulcus and right temporal pole. The ASD group showed decreased activation only in the left hippocampus.

In contrast, the NT group showed large activation decreases from Early to Late blocks predominantly in posterior areas, including those involved in learning (right thalamus, right hippocampus), sensory processing (bilateral postcentral gyrus), spatial processing (bilateral superior and inferior parietal lobules), pattern recognition (right inferior temporal gyrus), and visual processing (bilateral middle and inferior occipital gyri), as well as small decreases in frontal executive areas (left superior and middle frontal gyri). The NT group showed few areas of increased activation, including left middle occipital gyrus, bilateral precuneus, and right middle frontal gyrus.

The between-group contrast of Early>Late revealed that the NT group showed larger decreases over time (or the ASD group showed larger increases over time) in several areas, including right precentral and postcentral gyri, bilateral anterior and middle cingulate, left middle and superior temporal gyri, bilateral superior parietal lobule, bilateral supplementary motor area, left olfactory sulcus, left caudate, left superior and middle frontal gyri, and bilateral precuneus, as shown in Fig. 4 and Inline Supplementary Table 2. These findings indicate that with increased experience in the categorization task, NT participants reduced their reliance on parietal and occipital areas, while the ASD participants maintained their reliance on posterior areas and increased their recruitment of frontal, temporal, and parietal regions. Effects of age in activation changes over time are examined in Inline Supplementary Figure 2 and Inline Supplementary Table 3.

3.1.2 Percent signal change—The percent signal change analysis corroborated the hypothesis concerning a lesser decrease in activation over time in ASD. There was a significant Time × Group interaction ($F(2,60) = 4.3$, $p = 0.02$), reflecting that the ASD group increased in percent signal change from early to middle and late blocks, whereas the NT group decreased from early to middle and late, as seen in Inline Supplementary Table 4. There was neither a main effect of Group nor Time ($F<1$ for both).

3.1.3 Relation between ASD severity and activation adaptations over time—ASD symptom severity correlated with activation changes over time, such that individuals with *lower* ASD symptom severity showed *greater* decreases over time in temporal, posterior, subcortical, and frontal regions, shown in Fig. 5. Thus, those on the less-affected end of the ASD spectrum were more likely to show activation changes that were more similar to those shown by the NT participants. This relation was present between ADOS Total score and activation decreases in bilateral lingual gyrus, precuneus, right middle temporal gyrus, right middle occipital gyrus, bilateral cerebellum, right thalamus, bilateral insula, left middle and superior frontal gyri, right middle cingulate, and bilateral pallidum,

reported in Supplementary Table 2. The opposite effect (areas that showed a larger decrease in individuals with *more* severe ASD) was only found in the anterior cingulate, possibly reflecting reduced executive functioning in more severe ASD. These findings suggest that individuals with more severe ASD symptoms show larger disruptions in neural adaptation during implicit learning.

3.2 Functional Connectivity

3.2.1 ANOVA results—Participants in the ASD group had lower functional connectivity between frontal and posterior areas than did the NT group ($F(1,30) = 5.6$, $p = 0.02$), as shown in Fig. 6A. There was also a significant Time × Group interaction ($F(2,60) = 7.9$, $p = 0.0009$), reflecting that NT participants had increased synchronization from early to middle and late blocks, while the ASD group did not. Activation patterns in frontal and posterior areas became more synchronized over the course of learning only in NT participants. There was no effect of Time across groups ($F<1$). These findings suggest that functional connectivity was lower and less adaptable in the ASD group than the NT group.

Similar effects were found for non-frontal:posterior pairs, reported in Inline Supplementary Table 5. Functional connectivity was lower for ASD than NT participants ($F(1,30) = 4.8$, $p = 0.04$) and there was a Group × Time interaction ($F(2,60) = 14.2$, $p < 0.0001$), reflecting an increase from Early to Middle blocks for the NT group but not the ASD group. There was a marginal effect of Time overall ($F(2,60) = 2.5$, $p = 0.09$), driven predominantly by the NT participants. Thus, non-frontal:posterior pairs showed similar effects to frontal:posterior pairs, suggesting generalized reductions in inter-regional brain connectivity in ASD in this implicit learning task.

3.2.2 Relation between ASD severity and synchronization—To further test the link between brain synchronization and ASD severity, the correlation was measured between ASD symptom severity and functional connectivity in frontal:posterior pairs during Encoding blocks. Only ADOS Communication score negatively correlated with functional connectivity averaged across Frontal-Posterior Network Pairs ($r = -0.55$, $p < 0.05$). Individuals with *lower* ASD symptom severity showed *higher* functional connectivity, as shown in Fig. 6B. This relation reflects that participants on the less-affected end of the ASD spectrum showed higher synchronization, more similar to the NT participants, providing further evidence of a link between ASD and brain communication during implicit learning.

3.3 Behavioral Results

During the initial learning that occurred outside the scanner, ASD participants learned the task more slowly than NT participants, requiring more training runs to reach an accuracy criterion of 70% (ASD mean: 2.8; NT mean: 2.3; $F(1,30) = 4.3$, $p = 0.05$). This finding is in accordance with previous work that also reported slower learning of dot pattern prototypes in ASD (Vladusich *et al.*, 2010).

During the scanning session, there were no group differences in either error rates or reaction times ($F<1$ for both), reflecting similar performance between groups after the initial training session, as shown in Fig. 7. Both groups became faster at responding over time ($F(2,60) =$

6.0, $p = 0.004$), although they did not improve in accuracy ($F < 1$), which was above chance throughout the experiment. There were no significant interactions between Group and Time in error rates or reaction times ($F < 2$). Thus, the reported differences in brain activation and synchronization between groups occurred in the context of similar behavioral performance during the scanning session.

3.4 Summary

This study revealed evidence of reduced neural adaptation during learning in ASD. (1) ASD participants showed sustained or increased activation in the full task network over the course of learning, while NT participants had decreasing activation in parietal and occipital regions. Individuals with less severe ASD symptoms showed greater neural adaptation during learning. (2) The ASD group had overall lower functional connectivity (synchronization), compared to NT participants, particularly between frontal and posterior regions. Functional connectivity increased over time only for the NT participants. Individuals with less severe ASD symptoms had higher synchronization that was more similar to NT participants. (3) ASD participants learned the implicit task more slowly than NT participants in the training session, and the two groups had similar behavioral performance during the scanning session.

Discussion

The new findings here concerning atypical neural adaptations during implicit learning provide a possible account for some of the challenges of ASD. Unlike the NT participants, who demonstrated decreasing activation with time during the implicit dot pattern prototype task, the ASD participants maintained their reliance on the task network throughout the experiment and instead showed increasing activation in certain regions. Furthermore, the degree of the alteration in adaptation was proportional to the ASD symptom severity. Throughout the task the ASD group had lower functional connectivity (inter-regional activation synchronization) than the NT group, and this measure was also related to ASD symptom severity. Unlike the NT participants, who showed increasing functional connectivity over time, the ASD group's functional connectivity failed to increase, providing another indication of altered adaptation.

4.1 Adaptations in Activation

Over the course of learning, the ASD group did not show the same pattern of decreasing activation as did the NT group. The NT group showed decreases in predominantly posterior brain regions involved in visual processing (inferior occipital lobe, potentially a repetition priming effect to the repeated exposure to the visual stimuli) and spatial working memory and attention (superior and inferior parietal lobules, potentially reflecting decreasing attentional demands). These areas also showed decreases in an NT study of dot pattern prototype learning that was extended over several days (Little *et al.*, 2004). However, we also found increasing activation over time in a more posterior and inferior occipito-parietal cluster in the NT group, potentially reflecting increased recruitment, a characteristic of early learning (Little and Thulborn, 2005), or redistribution (Kelly and Garavan, 2005). Other regions showing this similar pattern of increased activation or recruitment in the NT group included several clusters in the precuneus, middle frontal, and caudate. Nearby clusters

showed a similar pattern in the ASD group, suggesting some overlap in the pattern of increasing activation over time between groups. The NT group in the current study also showed activation decreases in the thalamus and hippocampus, areas associated with learning and memory. Activation decreases in this network of areas in the NT participants suggest that their neural processes involved in task performance (encoding category members) became more efficient over time, achieving the same performance (with faster reaction times) using decreasing neural resources. There are several possible mechanisms by which such changes could arise. NT participants may have changed strategies as they learned the task. As they became more experienced with the novel category, they may have stopped updating their representation of that category, and therefore attended less to the dot patterns during Late blocks. It is also possible that this change in activation is related to a streamlining of the neural processing flow. Over repetitions of the task, the participation of non-essential processes (and the voxels in which they were implemented) may have declined. A third and related possibility is that activation changes arose out of enhanced communication between brain regions, such that the entire processing stream became more efficient.

The lack of increased neural efficiency in the ASD group was in accordance with previous findings in a social learning task (learning the visual and speech features associated with lying by an avatar) (Schipul *et al*., 2012). That study revealed a similar pattern of atypical neural adaptations during learning in ASD, reflected in increasing rather than decreasing activation over time, and lower and less adaptable synchronization. Here, increasing activation over time was found in executive function regions, including the anterior cingulate and superior and middle frontal gyri, suggesting increased executive control over task performance later in the experimental session, as well as in the putamen, which is associated with implicit learning. Decreasing activation over time in ASD was found only in the left hippocampus, contralateral to a cluster showing the same pattern in the NT group, suggesting that both groups reduced their reliance on explicit memory processes, perhaps no longer attempting the use of explicit strategies. The absence of a decrease in activation during learning in ASD in both studies may arise from altered inter-regional connectivity. In both cases, the ASD group had lower synchronization throughout the experiment, suggesting impaired communication between distal brain regions. Intact communication between regions may be necessary to streamline the information flow and reduce non-essential processing. Compromised inter-regional communication may have also limited the influence of frontal executive systems to exert control over posterior visuospatial processing centers. Without intact communication between executive centers and other regions, the ASD brain systems may have been precluded from developing a more efficient strategy during task performance. It is as yet unclear if reduced inter-regional communication in ASD limits neural adaptations at the level of improved strategies (i.e., a qualitative effect) or at the level of more streamlined neural processing (a more quantitative effect). Furthermore, recent cognitive modeling work of dot pattern prototype learning in ASD has also provided evidence that deficits in neural plasticity may account for atypical learning in ASD (Dovgopoly and Mercado, 2013).

The link between atypical neural adaptations over time and ASD was further demonstrated by a relation between ASD symptom severity score and activation decreases over time. Participants with lower ADOS Total scores (i.e., less severe ASD symptoms) had larger decreases in activation, a pattern more similar to the NT group. This may indicate that larger disruptions in neural adaptability may lead to greater behavioral impairments in individuals with ASD. However, it is also possible that impaired behavior may affect neural activation in this task, or that a third cause (such as impaired inter-regional communication) leads to disruptions in both brain and behavior. The evidence of a link between neural adaptability and symptom severity indicates the vital relevance of this neural characteristic to ASD. Neural adaptability may have potential as an outcome measure for future treatments or interventions.

4.2 Adaptations in Synchronization

The finding of lower functional connectivity in the ASD group, particularly between frontal and posterior regions, is consistent with the underconnectivity theory of autism (Just *et al.*, 2004, 2007). More specifically, the current functional connectivity findings add to previous findings of underconnectivity during social learning in ASD (Schipul *et al.*, 2012), and extends the theory to implicit dot pattern prototype learning. Reduced inter-regional communication in ASD may alter the learning process across a variety of tasks and everyday skills, potentially affecting both behavior and neural efficiency.

Synchronization was also less adaptable in the participants with ASD. The NT group showed increases in synchronization with time, a pattern reported in previous neuroimaging studies of learning in neurotypical participants (e.g., Büchel *et al.*, 1999; Toni *et al.*, 2002), indicating that inter-regional coordination improved over the course of learning. In contrast, the ASD group did not show an increase in synchronization over time, suggesting a more stable, rigid communication pathway between brain regions. This finding reflects that, in addition to not showing typical adaptations in activation levels, the ASD participants also did not show typical improvements in the synchronization of activation across regions during learning. The neural adaptability is impaired in ASD at multiple levels of neural function.

4.3 Behavioral Pattern of Implicit Learning

The behavioral results reported here suggest that people with ASD can perform dot pattern prototype learning but at a slower pace. The ASD participants required more training to reach criterion. However, after reaching that criterion, the ASD participants showed no differences in accuracy or reaction time from NT participants. A recent behavioral study also found that participants with ASD took longer to learn a dot pattern prototype task, but then showed intact prototype effects (Vladusich *et al.*, 2010). However, the atypical neural adaptations during implicit learning in the ASD group suggest that alterations do exist in this learning process. It is possible that the task difficulty here was low enough that individuals with ASD were able to overcome these deficits to show typical behavior after extended practice. If task difficulty were to increase, one might expect that behavioral performance would decrease in the ASD group relative to the NT group in the dot pattern prototype task. Another recent study found that individuals with ASD showed intact implicit learning in a

contextual cueing paradigm when spatial configurations were predictive, but not when only object-identity cues were present (Travers *et al.*, 2013). This may suggest that the spatial nature of the present task may be inherent to our finding of intact behavioral implicit learning in ASD.

The presence of intact behavioral learning in the ASD group despite atypical neural activation changes suggests that these neural adaptations may not be necessary for behavioral learning, with several potential implications. The ASD participants may have used an alternate strategy to learn the task (such as utilizing explicit processes). The neural adaptation seen in the NT group may reflect a changing strategy over time or waning interest in the task, which may not have occurred in the ASD group. The neural adaptations in the NT group may reflect increasing automaticity of the task, that may only impact behavior when resources are in greater demand (e.g. in the presence of a distractor task). Thus the pathway through which this neural disruption affects behavior in the disorder remains unclear. What is clear is that the neural processes underlying implicit learning are altered in ASD.

4.4 Clinical Implications

The neurally-based characterization of the disruption of learning in ASD provided by this study may inform intervention methods. For example, intervention methods may prove to be more effective if they incorporate explicit strategies to compensate for altered implicit learning abilities, particularly relating to social behaviors and language skills. Furthermore, this study suggests that neuroimaging can reveal atypical characteristics of learning in individuals with ASD even in cases where behavioral performance appears intact. Neuroimaging data can provide an additional fine-grained measure of learning processes and may be suitable for evaluating the efficacy of various intervention methods.

4.5 Limitations

While this study advances our understanding of neural adaptation during learning in ASD, several limitations of this study can be addressed in future studies. First, the participant sample was made up exclusively of adults (16 years and up) due to constraints of the scanning environment in special populations, and it would be informative to extend the analysis to younger samples, perhaps using alternative neuroimaging methodologies, such as electroencephalography. Second, there was no direct link between neural adaptation and behavioral improvement across participants (Inline Supplementary Table 6 reports correlations between reaction time changes and activation changes, revealing mainly negative relations, i.e. increases in activation with learning were associated with greater reaction time improvement). Alternative experimental designs, such as a more difficult implicit learning task or assessing the interference effect of a distractor task may provide useful information about the neural-behavioral linkage. A final limitation of this study is the limited sample size and somewhat lenient thresholding of voxel based analyses. However, these results are derived from a priori hypotheses based on previous work (Schipul et al., 2012) and here replicate those findings in a novel paradigm. Percent signal change analyses on a priori selected anatomical ROIs corroborate the voxel based analyses.

4.6 Conclusion

Implicit learning of a dot pattern prototype is altered in ASD, as indicated by slower behavioral learning, smaller activation decreases over the course of learning, lower synchronization throughout learning, and an absence of adaptations in synchronization during learning. Furthermore, ASD symptom severity was directly related to synchronization and neural changes with learning. Therapeutic approaches for ASD might benefit from making explicit the learning of various everyday skills that people without ASD learn implicitly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We sincerely thank the participants and families for their time and commitment to this research. We thank current and former members of the Center for Cognitive Brain Imaging for their assistance, particularly Diane Williams for insights into study design and Tim Keller for technical support. We thank Nancy Minshew and the Center for Excellence in Autism Research at the University of Pittsburgh for their assistance in participant recruitment, scheduling, and clinical assessments.

Funding: This research was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Autism Centers of Excellence Grant-HD055748; Training Grant T32HD40127 to S.E.S.) and the National Institute of Mental Health (Training Grant T32MH019983-11 to S.E.S.).

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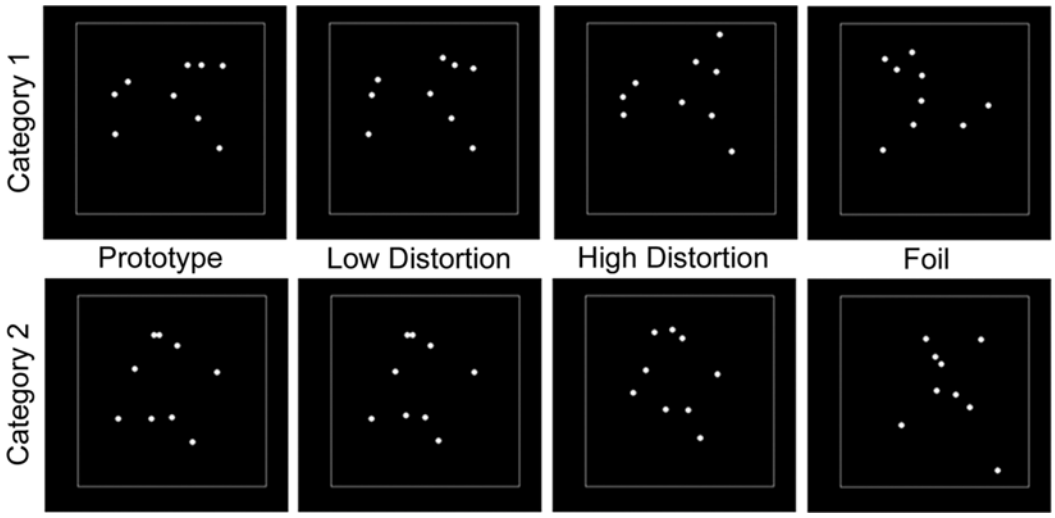

Figure 1.
For each category set, the prototype, and examples of low distortion, high distortion, and foil. [1.5-column][color]

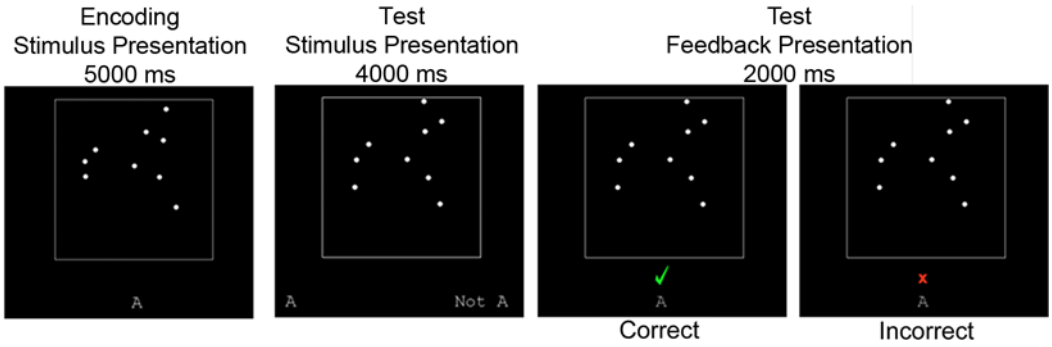

Figure 2.

An example of Encoding presentation, Test presentation, and Test correct and incorrect feedback. [1.5-column][color]

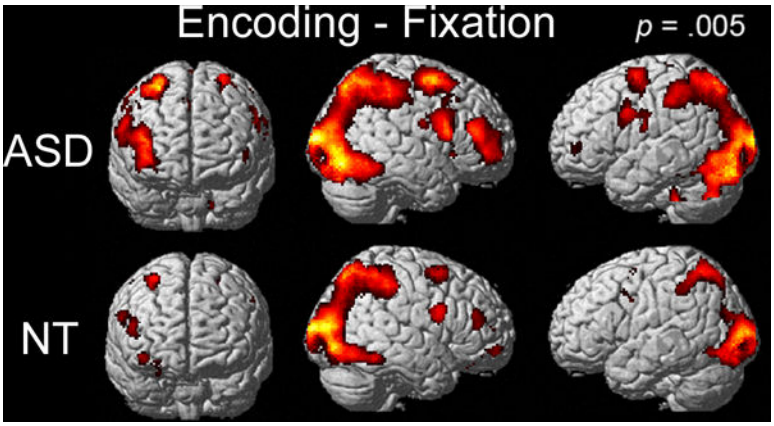

Figure 3.
Within-group contrasts showing regions that displayed activation for the Encoding-Fixation contrast. [1-column][color]

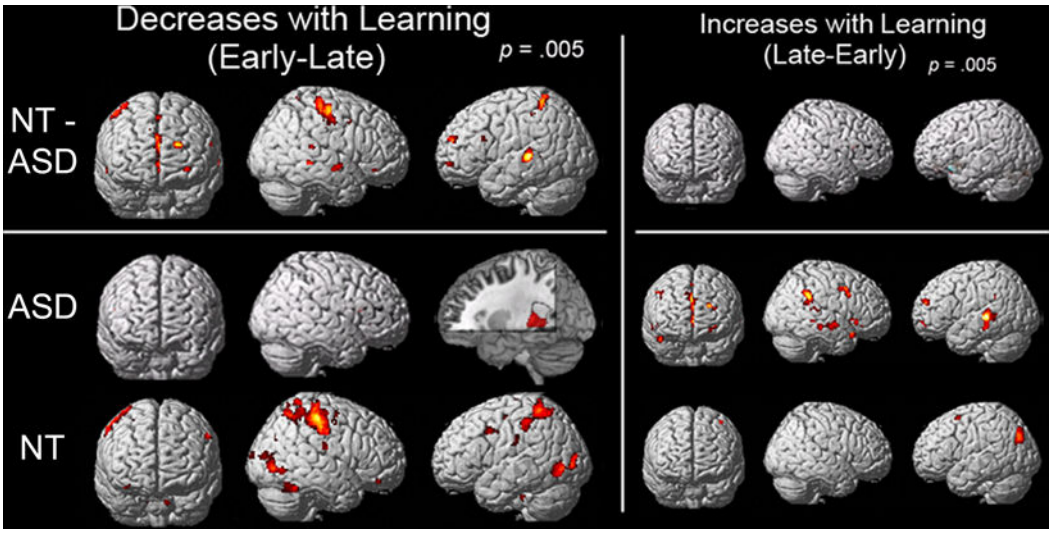

Figure 4.

Within- and between-group contrasts showing regions that displayed greater activation for Early Encoding blocks than Late Encoding blocks. The reverse contrast is also shown, indicating areas that showed greater activation for the Late blocks than the Early blocks. [1.5 column] [color]

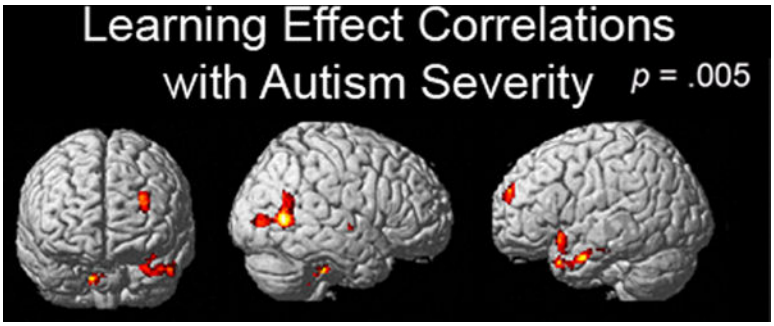

Figure 5.

Negative correlations between ASD symptom severity (as measured by ADOS Total scores) and activation decreases from Early Encoding blocks to Late Encoding blocks. [1-column] [color]

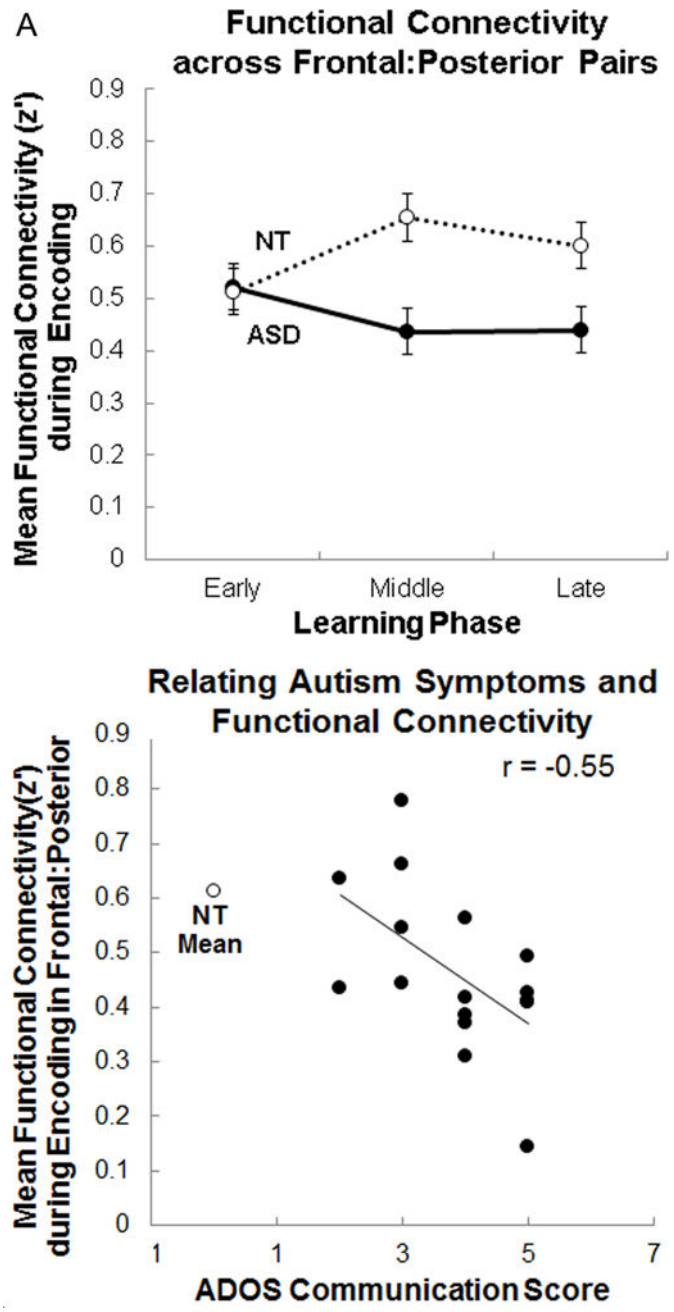

Figure 6.

(**A**) Functional connectivity values across frontal:posterior pairs during Encoding blocks. **(B)** Correlation between ASD symptom severity (ADOS Communication score) and frontal:posterior functional connectivity. [1-column]

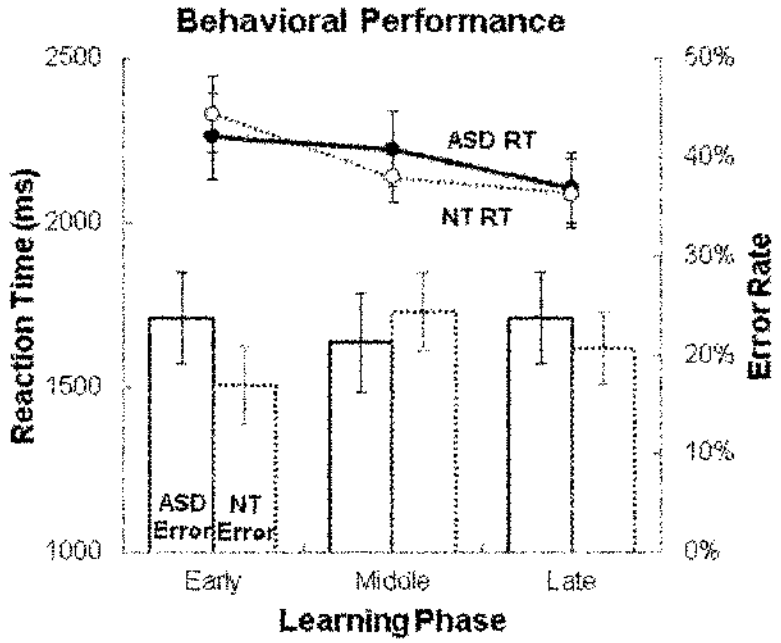

Figure 7.
Error rates and reaction times for the Test blocks. Error bars are standard errors. [1-column]

Table 1

Participant demographics

	ASD *n* = 16			NT *n* = 16			Group comparisons	
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	***t*(30)**	***P***
Age (years)	26.5	6.4	16–38	25.4	7.7	16–42	0.43	Ns
Verbal IQ	12.8	15.4	82–136	111.4	8.4	94–126	0.31	Ns
Full Scale IQ	13.8	12.4	88–131	113.8	8.5	101–126	0.02	Ns
Handedness (right:left)	13:3			15:1				
Gender (male:female)	14:2			14:2				
ADOS Communication	3.8	1.0	2–5					
ADOS Social	7.4	1.8	5–11					
ADOS Total	11.3	2.6	7–16					

Table 2

Dot displacement probabilities by distortion level

Distortion Level	Posner Level	Units Displaced				
		0	1	2	3–4	5–10
Low	3 bits/dot	.59	.20	.16	.03	.02
High	6 bits/dot	.00	.40	.32	.15	.13

Table 3

The order of presentation of the different blocks

*	**Familiar 1–2**		*	**New 1–2**		*	**New 3–4**		*	**Familiar 3–4**		*	**Familiar 5–6**		*	**New 5–6**	
	E	T		**E**	**T**		**E**	**T**		E	T		E	T		**E**	**T**

E = Encoding block; T = Test block; * = Fixation; Familiar = category set seen in the training session; New = category set distinct from that used in training. All New blocks are bolded because only they are included in the present analysis.