# Structural learning difficulties implicate altered hippocampal functioning in adults with Autism Spectrum Disorder

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## Abstract

Structural Learning is fundamental to the formation of cognitive maps that are necessary for learning, memory, and spatial navigation. It also enables successful navigation of the social world, which is something that individuals with Autism Spectrum Disorder (ASD) find particularly difficult. To master these situations, a person needs to bind pieces of information to one another and to consider the context in which experiences happen. Such binding is a capacity of the hippocampus. Although altered hippocampal function has for long been suspected to play a role in the aetiology of ASD, the relevant evidence has remained inconclusive because few behavioural tests that are known to specifically necessitate preserved hippocampal function have been employed in studies of ASD. To address this gap in the literature, a total sample of 57 pairs of age and ability matched ASD and comparison participants was divided into three subsamples who were asked either to complete Structural Learning, or one of two configural learning control tasks (Biconditional Discrimination and Transverse Patterning) drawn from animal research. As predicted, ASD adults demonstrated specific difficulty with Structural Learning but not with other forms of configural learning. These differences were not attributable to decreased attentional shifting or increased perseveration, which would have indicated atypical frontal modulation of hippocampal processes. Instead, the observations implicate atypical hippocampal functioning as the source of structural learning difficulties in ASD. The data suggest that disturbances in domain-general cognitive processes such as Structural Learning, caused by altered hippocampal function, play a critical role in the aetiology of ASD.

**Keywords:** Autism Spectrum Disorder, hippocampus, structural and configural learning, cognitive maps

**General scientific summary**

The role of hippocampal abnormalities in the aetiology of Autism Spectrum Disorder (ASD) has remained unclear because few studies have employed tasks that necessitate hippocampal function. This study confirms hippocampal involvement in ASD by demonstrating specific impairments on a particular kind of configural learning (Structural Learning) that is known to be hippocampus dependant.

## Introduction

An organisms' environment comprises a large number of elements (colours, shapes, objects, people, etc.) that can combine in a seemingly infinite number of ways to constitute unique experiences. The central nervous system thus faces the computational challenge of discriminating among experiences that share a great number of elements whilst extracting commonalities that serve effective adaptation to new situations. This problem is evident across numerous functional domains, ranging from spatial navigation and memory through imagination and creativity to social interaction and the use of language (e.g., Rubin et al., 2014). For example, when an animal learns to navigate its surroundings to forage for food, it needs to discriminate among various landmarks, represent the locations that have already been searched, and extract commonalities among the locations that have been visited to effectively seek out new sources of food. Similarly, humans, and other species that must navigate complex social environments, need to discriminate a myriad of social-communicative behaviours (e.g., facial expressions, gestures, vocalisations, etc.) across a large number of pragmatic contexts in order to develop an understanding of social norms, conventions and interpersonal relations that govern successful interactions with others. The hippocampus has for long been known to mediate these computational demands in the context of spatial navigation, learning and memory (O'Keefe & Nadel, 1978; Rudy & Sutherland, 1995; Sutherland & Rudy, 1989) and more recently it has also been implicated in higher order cognitive domains such as imagination, language and social interaction (Rubin et al., 2014; Schiller et al., 2015). This raises the possibility that hippocampal abnormalities play a critical role in the aetiology of Autism Spectrum Disorder (ASD), which is characterised by abnormalities across many of these functional domains.

ASD is a lifelong neurodevelopmental disorder that is clinically defined by impairments in social interaction and repetitive and stereotyped behaviour (American

Psychiatric Association, 2013). It affects approximately 1% of the population (Baird et al., 2006) and is frequently associated with significant language (Loucas et al., 2008; Tager-Flusberg & Joseph, 2003) and intellectual impairments (Baird et al., 2006; Idring et al., 2015; Kim et al., 2011; Yeargin-Allsopp et al., 2003) as well as mental health difficulties, such as depression, and anxiety (Croen et al., 2015; Simonoff et al., 2008). Sub-clinically, ASD is also associated with abnormalities in a number of cognitive domains, including learning and memory (see Boucher & Bowler, 2008), which has led to the suggestion that atypical hippocampal function plays a critical role in the aetiology of the disorder (Boucher & Warrington, 1976; Bowler et al., 2011; DeLong, 1992; Waterhouse et al., 1996). For instance, consistent with altered hippocampal function, individuals with ASD have difficulties remembering the temporal order of sequentially presented stimuli (Bigham et al., 2010; Gaigg et al., 2014; Ni Chuileann and Quigley, 2013; Poirier et al., 2011). Their episodic memory for past events as well as their ability to imagine themselves in the future (i.e., episodic future thinking; Tulving, 2002) is also compromised (Bowler et al., 2007; Lind et al., 2014a, b; Terrett et al., 2013) and they have difficulties with spatial memory (Bowler et al., 2004, 2014; Cooper et al., 2015; Ring et al., 2015, 2016) and spatial navigation (Lind et al., 2013, 2014a; Pellicano et al., 2011). Beyond studies of learning and memory, the hippocampus has also been implicated in ASD through animal models, which demonstrate that lesions to the medial temporal lobes including the hippocampus result in social impairments and repetitive behaviours akin to those seen in ASD (Bachevalier, 1994, 1996). Moreover, the extent of hippocampal and medial temporal lobe damage is thought to account for the heterogeneity across the autism spectrum, particularly with respect to general intellectual functioning (Bachevalier, 1994; Bachevalier & Loveland, 2006; Waterhouse, 2013).

The evidence outlined above implicates hippocampal abnormalities in ASD only indirectly and the observations can equally well be explained with reference to abnormalities in other brain areas, particularly the frontal lobe executive system (Hill, 2004a, b; Minshew & Goldstein 1998). In fact there is now a broad consensus that the neuropathology of ASD is not localised to particular regions but that it involves abnormalities in inter-regional connectivity and broader network function instead (Minshew & Keller, 2010; Uddin, Supekar & Menon, 2013). It is thus not surprising that direct examinations of hippocampal morphology in ASD have yielded inconsistent results, with some studies reporting no differences in hippocampal volume between ASD and comparison groups (Haznedar et al., 2000) whilst others have reported increased (Schumann et al., 2004) or decreased volumes (Nicolson et al., 2006; see Stigler et al., 2011 for a review). The few existing functional imaging studies have been equally inconclusive with a study by Solomon et al. (2015) observing no evidence for ASD related hippocampal abnormalities during a transitive inference task, whilst Cooper et al. (2017) observed reduced hippocampal connectivity during the retrieval but not the encoding of specific object features (see also Gaigg et al., 2015). In the context of this limited literature, it is important to shed further light on particularly those hippocampal processes in ASD that are known to operate across functional domains, and to use tasks that are specifically sensitive to hippocampal function (cf. Solomon et al., 2015). The current study addresses this aim by borrowing a task from the non-human animal literature to examine a domain-general learning process known as *Structural Learning*.

Structural Learning constitutes a sub-type of configural learning that necessitates the processing of spatial (or temporal) relations among the elements of an experience and, thus, critically depends on the hippocampus (Aggleton et al., 2007, 2009, 2010; Browning & Gaffan, 2008; Butt & Bowman, 2002). For example, Structural Learning is necessary for an animal to learn that yellow moss to the right of a gnarled branch at the base of a tree marks a

safe source of food whereas other spatial arrangements of these features signal no food or even danger. Similarly, Structural Learning is involved when we learn that certain behaviours in one pragmatic context facilitate social affiliation with certain individuals whilst the same behaviours in a different context or in relation to different individuals can lead to confrontation. If atypical hippocampal function plays an important role in the presentation of ASD, it follows that Structural Learning should pose particular difficulties, whereas other forms of configural learning that pose similar processing demands but do not necessitate hippocampally mediated processing of spatial-temporal information, should be preserved (Aggleton et al., 2007, 2009; Sanderson et al., 2006). For example, *Biconditional Discrimination* also requires the processing of specific relations among the elements of a stimulus but unlike in Structural Learning, the spatial or temporal configuration of these relations is irrelevant. Returning to the earlier example, Biconditional Discrimination would therefore allow an animal to learn that the combination of yellow moss and a gnarled branch at the base of a tree signals a source of food so long as the spatial arrangement of these features is irrelevant. Another example of configural learning that does not rely on hippocampally mediated processing of spatial-temporal information is *Transverse Patterning*, which requires learning of non-transitive binary relations among three stimuli such as in the well-known game "*rock-paper-scissors*" where *paper* beats *rock*, *rock* beats *scissors* and *scissors* beat *paper*.

To test the prediction that specifically *Structural Learning*, but not *Biconditional Discrimination* or *Transverse Patterning* is impaired in ASD, the current study adopts a paradigm by Sanderson et al. (2006), who examined the consequences of hippocampal lesions on these three types of configural learning in rats. In their experiment, independent groups of rats first learned to discriminate between pairs of stimuli that were constructed to specifically probe each of the three learning processes. Stimuli were affixed to either side of a

partition wall within a water tank in which the rats learned to find a submerged platform by swimming towards one of the stimuli. Once the rats had successfully learned the discriminations across a number of training sessions, half received hippocampal lesions and the other half received sham lesions. Following recovery, rats needed to re-learn the original discriminations across another set of training blocks and whilst hippocampal lesions had no effects on *Biconditional Discrimination* and *Transverse Patterning*, they led to significant reductions in learning across all blocks of *Structural Learning* (Sanderson et al., 2006). Of interest, however, was also that the response to mirror-image stimuli in *Biconditional Discrimination* was superior in rats with hippocampal lesions compared to sham lesions. This was assessed by ratio scores setting performance on mirror images in relation to performance on studied trials (mirror images/(mirror images + studied)). Rats with hippocampal lesions showed higher ratio scores compared to sham lesioned rats. Recall that in *Biconditional Discrimination*, the spatial arrangement of stimuli is irrelevant such that B | W and W | B would both be correct whereas in *Structural Learning* this spatial arrangement strictly defines the correct response. As the authors explain, the automatic employment of *Structural Learning* during *Biconditional Discrimination* makes the learning of mirror-image stimuli more difficult because the spatial arrangement of stimuli is processed as critical. Because hippocampal damage reduces sensitivity to the structural arrangement of stimulus elements, the level of performance on mirror-image stimuli in *Biconditional Discrimination* provides an additional measure of hippocampal function. A similar test can be included for *Structural Learning* where performance on re-paired stimuli of previously studied images is set in relation to studied images (re-paired/( re-paired + studied)). Similarly to *Biconditional Discrimination*, reduced learning of the structural arrangement of the mirror images presented in *Structural Learning* should lead to better performance on re-paired trials and higher ratio scores for individuals with atypical hippocampal function.

Based on the literature reviewed above, the first aim of the present study was to adapt the task by Sanderson et al. (2006) to test the prediction that ASD would be characterised by specific impairments in *Structural Learning*, but not *Biconditional Discrimination*, or *Transverse Patterning*. In addition, we expected better performance in novel test trials (re-paired for Structural Learning and mirror images for Biconditional Discrimination) and higher ratio scores for ASD compared to TD participants. Given that human participants are likely to employ various executive control processes to regulate their learning, a third aim was to control for the possible moderating role of executive functions in these configural learning processes.

## Materials and Methods

### Participants

Since no means, standard deviations, or effect sizes were available in Sanderson et al. (2006), sample sizes were based on the size of samples previously used in studies of this kind. Sanderson et al. (2006) tested six rats on average in each group for each of the three tasks. To increase statistical power to detect a possible between-group difference between ASD and TD individuals because of the heterogeneity of ASD samples, overall 114 adults took part in either of three tasks, resulting in 19 typically developing (TD) and 19 ASD adults each performing *Structural Learning*, *Biconditional Discrimination*, or *Transverse Patterning*. The sub-samples assigned to each of the experimental tasks were closely matched on gender ($X^2_{max} < 2.18$, $p_{min} > .14$), chronological age (CA; max. Cohen's $d < 0.12$), Verbal (VIQ; max. Cohen's $d < 0.23$), Performance (PIQ; max. Cohen's $d < 0.06$), and Full-scale Intelligence Quotient (FIQ; max. Cohen's $d < 0.12$) as measured by the third or fourth version of the Wechsler Adult Intelligence Scale (WAIS-III$^{UK}$ or WAIS-IV$^{UK}$; The Psychological

Corporation, 2000, 2008). Also, across the three experimental tasks there were no significant differences in the sample characteristics (all relevant *p* values > .49; see Table 1).

Table 1: *Participant characteristics for ASD and TD groups, split up by task – Structural Learning, Biconditional Discrimination, and Transverse Patterning.*

| | **TD** | **ASD** | | | |
|---|---|---|---|---|---|
| | ***M* (*SD*)** | ***M* (*SD*)** | ***t*(df)** | ***p*** | **Cohen's *d*** |
| **Structural** | (12m, 7f) | (16m, 3f) | | | |
| **Age (years)** | 41.06 (13.69) | 42.02 (13.30) | 0.22 (36) | .83 | 0.07 |
| **VIQ**[a] | 110 (14.0) | 111 (16.8) | 0.14 (36) | .89 | 0.04 |
| **PIQ**[b] | 105 (15.5) | 104 (16.8) | 0.06 (36) | .95 | 0.02 |
| **FIQ**[c] | 108 (14.0) | 108 (17.0) | 0.15 (34) | .88 | 0.05 |
| **CTT2**[d] | 0.37 (0.7) | 0.26 (0.6) | 0.52 (36) | .61 | 0.17 |
| **Biconditional** | (16m, 3f) | (15m, 4f) | | | |
| **Age (years)** | 43.57 (11.88) | 43.85 (13.03) | 0.07 (36) | .94 | 0.02 |
| **VIQ**[a] | 109 (14.2) | 110 (18.0) | 0.23 (36) | .82 | 0.07 |
| **PIQ**[b] | 105 (16.1) | 105 (17.1) | 0.00 (36) | 1 | 0.00 |
| **FIQ**[c] | 107 (15.3) | 108 (17.1) | 0.28 (33) | .79 | 0.09 |
| **Transverse Patterning** | (15m, 4f) | (16m, 3f) | | | |
| **Age (years)** | 41.77 (12.81) | 43.37 (12.85) | 0.38 (36) | .70 | 0.12 |
| **VIQ**[a] | 112 (12.7) | 115 (16.1) | 0.71 (36) | .49 | 0.23 |
| **PIQ**[b] | 107 (13.4) | 108 (15.0) | 0.17 (36) | .87 | 0.06 |
| **FIQ**[c] | 109 (14.4) | 111 (16.0) | 0.33 (29) | .74 | 0.12 |
| **Total sample** | | | | | |
| **AQ**[e] | 15.05 (6.54) | 35.34 (7.62) | 15.96 (111) | .00 | 3.00 |
| **AQ range** | 1 - 28 | 18 - 49 | | | |

*Note*. [a]Verbal IQ (WAIS-III$^{UK}$ or WAIS-IV$^{UK}$). [b]Performance IQ (WAIS-III$^{UK}$ or WAIS-IV$^{UK}$). [c]Full-scale IQ (WAIS-III$^{UK}$ or WAIS-IV$^{UK}$). [d]Color Trails Test Trial 2. [e]Autism-Spectrum Quotient.

Participants were all native English speakers recruited from a database of participants with whom the Autism Research Group at City, University of London is in regular contact. All ASD adults had been diagnosed according to DSM-IV-TR (American Psychiatric Association, 2000) criteria by experienced clinicians and it was possible to administer the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) to 48 of the 57 participants. In all cases this observational measure corroborated impairments in social communication behaviors commensurate with ASD, and in line with the expected sensitivity of the instrument (see Hus & Lord, 2014), 44 individuals (92%) met the cut-off for the *Reciprocal Social Interaction* domain and 39 individuals (81%) met the cut-off for the *Communication* domain. Because of time constraints on the day of testing, it was not possible to administer the ADOS to nine participants (2 in Structural Learning, 6 in Biconditional Discrimination and 1 in Transverse Patterning), but since available records confirmed their clinical diagnosis all participants were retained for analysis. Furthermore, participants in both groups (except for one ASD individual on Biconditional Discrimination) completed the Autism-Spectrum Quotient (AQ; Baron-Cohen et al., 2001), which provides a self-report measure of autistic-like traits. This confirmed significantly higher scores for the ASD compared to the TD group ($t$ = 15.2, df = 111, $p$ < .001, Cohen's $d$ = 2.9) and average scores (ASD: $M$ = 35.3, $SD$ = 7.6; TD: $M$ = 15.1, $SD$ = 6.5) fell well within the expected ranges recently reported in a comprehensive meta-analysis (Ruzich et al., 2015)[1]. In the current study, six out of 56 persons with ASD (10.71 %) scored below the cut-off score of 26 suggested by Woodbury-Smith, Robinson, Wheelwright and Baron-Cohen (2005) and one of the 57 TD individuals (1.75%) scored above this cut-off. We did not use AQ scores as an inclusion/exclusion criterion because it is not generally used to establish a diagnosis and

[1] For ease of reference, Ruzich et al., (2015) report an AQ range of 27.6 to 41.1 for clinical samples and 11.6 to 20.0 for non-clinical samples.

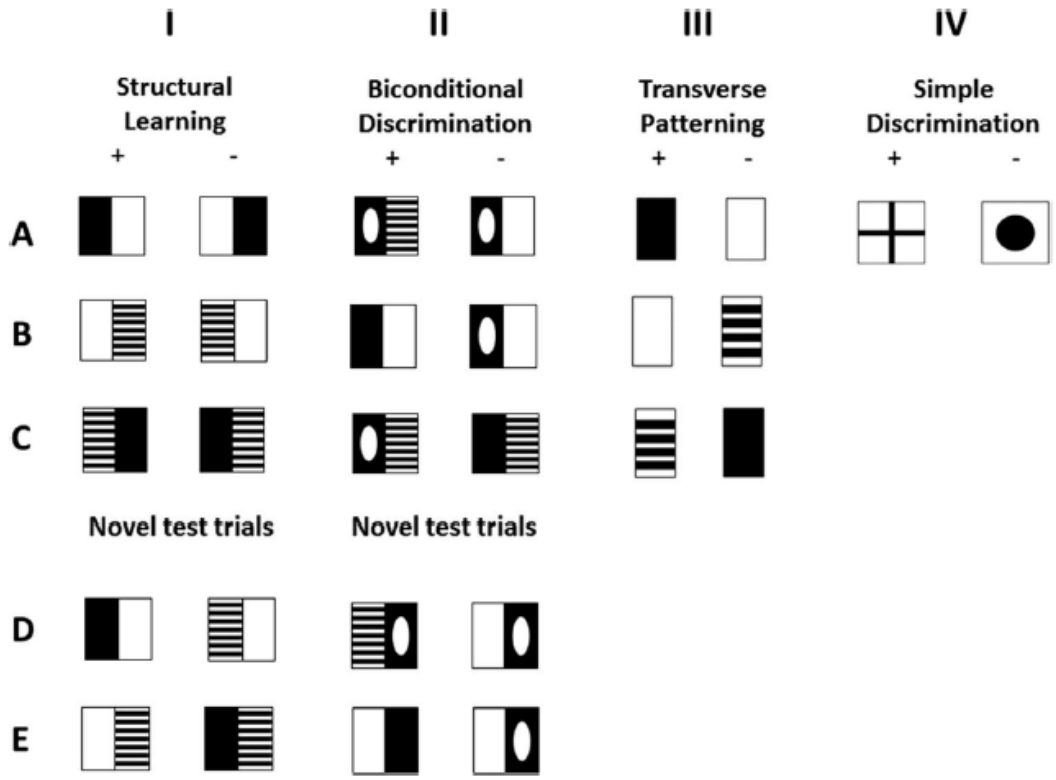
because preserving a wide range of self-reported autistic-like traits in both groups was important for the correlation analyses reported below.

TD individuals did not report taking psychotropic medication or a personal or family history of a psychological or neurodevelopmental disorder including ASD. Twelve of the ASD participants (4 in Biconditional Discrimination, 5 in Structural Learning and 3 in Transverse Patterning) reported taking antidepressants of whom three (2 in Biconditional Discrimination and 1 in Strucural Learning) also reported prescriptions for antipsychotics. A further two ASD participants (1 in Structural Learning and 1 in Transverse Patterning) reported taking only antipsychotics. Participants were not asked to stop taking their medication before participation. All participants were reimbursed for their time and travel costs with standard university fees. Informed consent was taken prior to participation. This study was approved by City, University of London's ethics committee (name: Complex visual discrimination in Autism Spectrum Disorder; approval number: PSYETH 11/12 017), and procedures adhere to the ethical guidelines set out by the British Psychological Society.

**Materials**

The materials and procedures were adapted from Sanderson et al. (2006) and similar rodent studies (e.g., Aggleton et al., 2007) and involved minimal verbal instructions. Black and white images (see Figure 1) were presented on a touch-sensitive 12-inch laptop-screen. A detailed overview of the stimuli and reinforcement contingencies is provided in the supplemental materials. In order to take frontal lobe executive processes into consideration, the Colour Trails Test (CTT; D'Elia et al., 1996) was administered and the number of errors on part 2 (hereafter CTT2) of this task was taken as an index of frontal lobe executive function as this has been shown to be sensitive to frontal lobe damage (Kopp et al., 2015).

Figure 1. *Examples of stimuli for Simple Discrimination (Column IV), which was part of all three tasks. Structural Learning (Column I) with test trials presenting re-paired stimuli in Block 5 in Row D and E, Biconditional Discrimination (Column II) with test trials presenting mirror images in Rows D and E, and Transverse Patterning (Column III). The stimuli presented below the plus sign are reinforced in the example.*




**Procedure**

To familiarize participants with the general task procedures, the experiment began with a Simple Discrimination task (Figure 1 Column IV), in which participants simply learned that touching one of two distinct images on the screen would result in the presentation of either a smiling cartoon face or a frowning cartoon face that indicated that a correct or incorrect response had been made respectively. Age and ability matched subgroups of ASD and TD participants then took part in either *Structural Learning*, *Biconditional*

*Discrimination*, or *Transverse Patterning* that included also a number of interspersed Simple Discrimination trials to ensure participants maintained their attention on the task and did not perseverate on certain screen locations in their responses (Sanderson et al., 2006). The experimenter stayed in the room with the participant to be available for questions.

Each task (*Structural Learning*, *Biconditional Discrimination* and *Transverse Patterning*) consisted of five blocks, across which relevant stimuli were successively introduced until participants either demonstrated reliable acquisition of all necessary stimulus contingencies or failed to reach a learning criterion within a pre-determined maximum number of trials (see details below). After each block of trials there was a brief pause that participants could terminate to continue the task by pressing a pause button on the laptop-screen. On every trial, two images were presented simultaneously and participants were asked to pick the correct image by touching it. The same smiling or frowning cartoon faces as during the Simple Discrimination practice trials served as feedback and participants were told to aim for as many correct responses as possible. Which images were reinforced, the screen locations of reinforced stimuli and the block in which stimuli were introduced were all fully counterbalanced across participants.

Every trial started with the presentation of a blank screen for 1 s, followed by the two images on the left and right side of the screen, which remained until participants touched one of them. Feedback stayed on-screen for 1.5 s, after which the next trial started. In every block, participants had to learn to a pre-determined criterion. If the criterion was reached, the task continued with the next block. Otherwise the block was presented a maximum of three times before the program continued automatically to the next block. For example, in Block 1, participants received 10 experimental trials and two Simple Discrimination trials and needed to achieve 80% accuracy on the experimental trials and 50% accuracy on the Simple Discrimination trials. Because Block 5 was the final test block, it was only presented once to

participants and there was no criterion. Tables S1 – S3 in the supplemental material provide details of all trial numbers and learning criteria for the three experimental conditions. For simplicity, we note here only that every task started with the presentation of one pair of experimental images and new pairs were then added across successive blocks, until all shapes were repeated in Blocks 4 and 5. In addition, in Block 5 of *Structural Learning* studied images were presented intermixed with new re-paired images (see Figure 1 Column I Rows D & E) and in *Biconditional Discrimination* mirror-images of studied stimuli were introduced (see Figure 1 Column II Rows D & E). Figure 1 provides an overview of the experimental materials involved in each of the three conditions and we briefly outline critical details of each of them below.

*Structural Learning*

In *Structural Learning* (Figure 1 Column I Rows A, B & C) participants were successively introduced to three pairs of compound stimuli that were mirror images of each other. The images were made up of simple patches of white, black, or striped. Participants were asked to learn to discriminate between the mirror images, which required them to bind the two patches of an image and represent their specific spatial configuration. For instance, participants needed to learn that *black* and *white* constituted a correct image only if the *black* patch was on the left side of the *white* patch (Row A). When *white* was presented with *striped*, participants needed to know that only the shape with *white* on the left side of *striped* was correct (Row B), and so on. Image pairs were introduced consecutively across three blocks. In Block 4 all three image pairs were presented in a mixed random order and in Block 5 previously studied image pairs were presented along with re-paired trials that had never been presented together previously (see Figure 1 Column I Rows D & E). For example, the previously studied pairs *black/white* vs. *white/black* (Row A) and *white/striped* vs.

*striped/white* (Row B) were recombined in a novel test trial that asked participants to choose between *black/white* vs. *striped/white* (Row D) or *white/striped* vs. *white/black*. Re-paired trials were included to establish whether the structural arrangement of the stimuli had been fully processed and would thus transfer to new trials that could not be solved through simpler learning processes.

*Biconditional Discrimination*

In *Biconditional Discrimination* (Figure 1 Column II), participants were asked to discriminate between four pairs of compound images that were again made up of simple patches such as *black*, *white*, *striped*, and *black with a white ellipse*. As in *Structural Learning*, pairs were introduced consecutively across three blocks, with two new pairs introduced in Block 3. Blocks 4 and 5 again presented all image pairs in random order with Block 5 including novel test trials that comprised mirror images of the studied images (Rows D & E). Unlike in *Structural Learning*, the spatial configuration of the images was irrelevant and of interest was how readily learning would transfer to the new stimulus configurations.

*Transverse Patterning*

In *Transverse Patterning* (see Figure 1 Column III), participants needed to discriminate between three pairs of simple patches (*black*, *white* & *striped*) in which the correct response was determined by the combination of patches that was presented in a given trial. The rules were analogous to that of the hand game rock-paper-scissors, where rock beats scissors, scissors beat paper, and paper beats rock. Participants needed to learn that *black* was correct when presented with *white* (Row A), that *white* was correct when presented with *striped* (Row B) and that *striped* was correct when presented with *black* (Row C). Again, the

three pairs were introduced consecutively across three blocks and then presented together in a random order in Blocks 4 and 5.

**Statistical analysis**

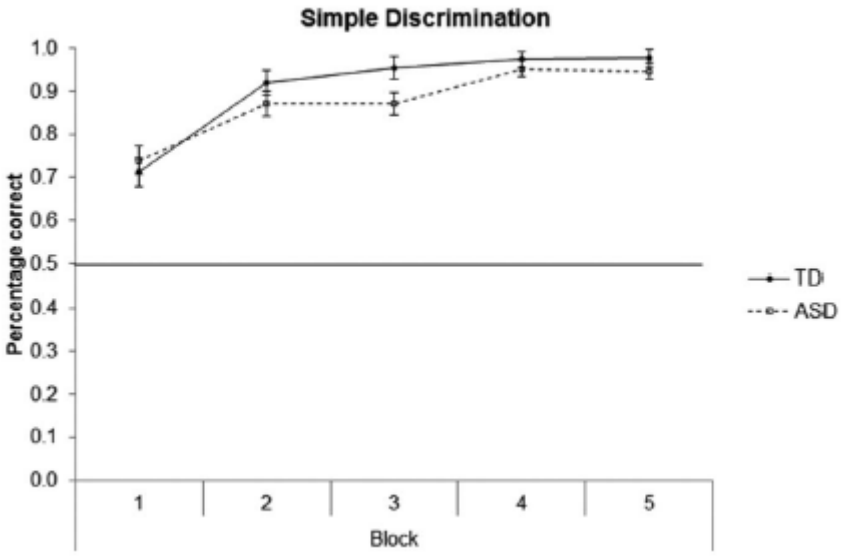
The data were analysed in SPSS version 23 with Chi-Squared Tests for nominal data, and bivariate correlations, t-tests, and repeated measures ANOVAs and ANCOVAs for interval data. In case the Sphericity assumption was violated in ANOVAs, the Greenhouse Geisser correction (GGC) was used. Significant effects were clarified with Bonferroni-corrected post-hoc tests and within subjects contrasts were examined to determine whether learning was characterised by non-linear trends. The significance level was chosen at .05 for all tests. Cohen's *d* and partial eta squared are reported as measures of effect size.

**Results**

**Simple Discrimination**

Accuracy scores (percentage correct) for the Simple Discrimination trials that were included in all trial blocks are presented in Figure 2. Performance for both groups was significantly above chance in all five blocks, all $t > 6.35$, all $p < .001$. A 2 (Group [ASD, TD]) x 3 (Task [*Structural Learning, Biconditional Discrimination, Transverse Patterning*]) x 5 (Block [1, 2, 3, 4, 5]) repeated measures ANOVA revealed a significant main effect of Block, $F(1.91,206.60) = 41.06$, $p < .001$, $\eta_p^2 = .28$, GGC, but no other significant main effects or interactions, $F_{max} < 1.80$, $p_{min} > .17$, $\eta_p^2{}_{max} < .02$, indicating that learning over blocks did not differ between groups or Task.

Figure 2. *Accuracy as percentage correct for Simple Discrimination for ASD and TD individuals for the five blocks of the tasks averaged across Structural Learning, Biconditional Discrimination, and Transverse Patterning. The horizontal line indicates chance performance. The data are presented as mean ± SEM.*




**Structural Learning**

***Learning***

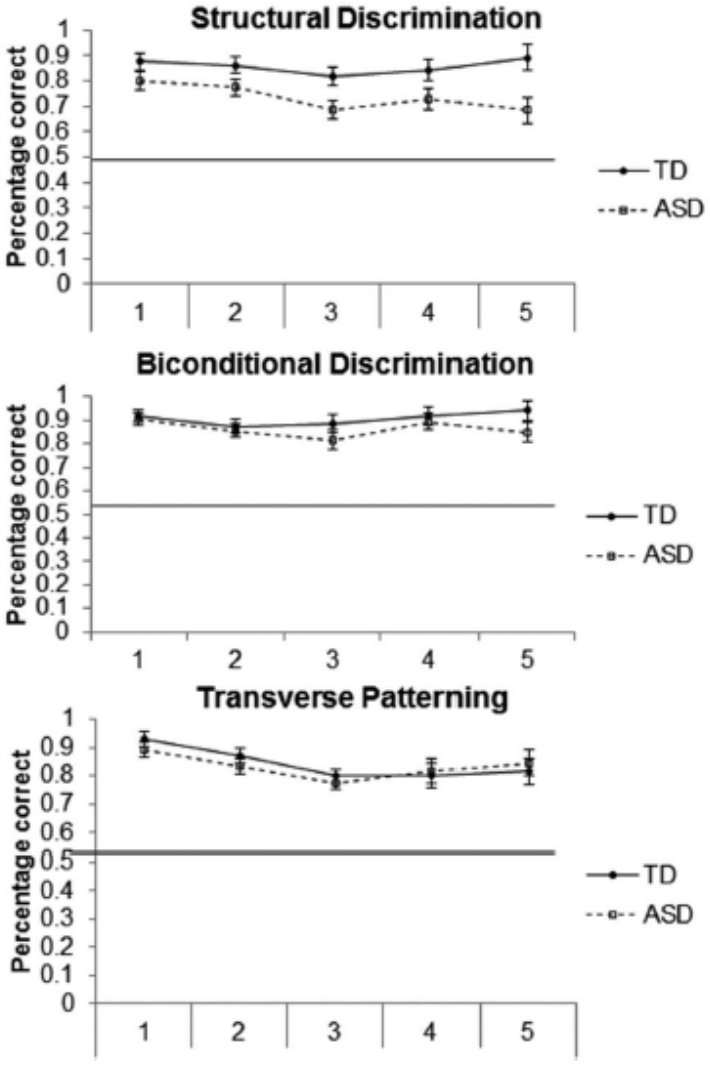
Accuracy scores (percentage correct) are presented in Figure 3, and they were analysed with a 2 (Group [ASD, TD]) x 5 (Block [1, 2, 3, 4, 5]) repeated measures ANOVA, which showed a significant main effect of Group, $F(1,36) = 6.74$, $p < .05$, Cohen's $d = 0.84$, 95 % CI(0.16, 1.49), with lower performance of the ASD ($M = 0.73$, $SD = 0.15$) compared to the TD group ($M = 0.86$, $SD = 0.15$) overall. A significant main effect of Block, $F(2.73,98.25) = 3.64$, $p < .05$, $\eta_p^2 = .09$, GGC that was characterised by a quadratic trend ($F(1,36) = 6.22$, $p < .05$, $\eta_p^2 = .15$), demonstrated decreases in performance from Blocks 1 – 3 ($p < .05$) with no further significant changes through Blocks 4 and 5. No Block x Group interaction, $F(2.73,98.25) = 2.10$, $p = .11$, $\eta_p^2 = .06$, GGC, was found. Some individuals in both groups needed three attempts or did not reach criterion at a certain block (see Table 2).

Table 2. *Numbers of individuals with Autism Spectrum Disorder (ASD) and typical development (TD) that needed three attempts or did not reach criterion at a certain block - sorted by task: Structural Learning, Biconditional Discrimination, and Transverse Patterning.*

| | **Structural Learning** | | **Biconditional Discrimination** | | **Transverse Patterning** | |
|---|---|---|---|---|---|---|
| **Block** | **TD** | **ASD** | **TD** | **ASD** | **TD** | **ASD** |
| **1** | 2 | 4 | 0 | 2 | 1 | 2 |
| **2** | 4 | 5 | 3 | 3 | 0 | 3 |
| **3** | 8 | 11 | 4 | 7 | 8 | 4 |
| **4** | 5 | 9 | 4 | 3 | 7 | 5 |

Following Sanderson et al. (2006), the strictest test of Structural Learning occurs in Block 4 where participants see all three image pairs in randomised order. To test whether participants from both groups acquired Structural Learning or just learned one or two out of the three pairs, we compared Block 4 performance against chance level separately for each of the three pairs in both groups. We ranked performance for each individual on each of the pairs according to best, middle, and worst to see if participants' worst discrimination was greater than chance. Whereas TD individuals performed significantly better than chance on all three discriminations ($M_{min}$ = 0.72, $SD_{min}$ = 0.25), all $p < .01$, the ASD individuals' performance was greater than chance only for the two best discriminations ($M_{min}$ = 0.73, $SD_{min}$ = 0.23), both $p < .001$. Their worst discrimination was not significantly different from chance ($M$ = 0.58, $SD$ = 0.28), $p$ = .24, suggesting that they did not acquire Structural Learning, but that they rather used some other strategy to perform the task.

Figure 3. *Accuracy as percentage correct for Structural Learning (top), Biconditional Discrimination (middle), and Transverse Patterning (bottom) for ASD and TD individuals for the five blocks of the tasks. The horizontal line indicates chance performance. The data are presented as mean ± SEM.*

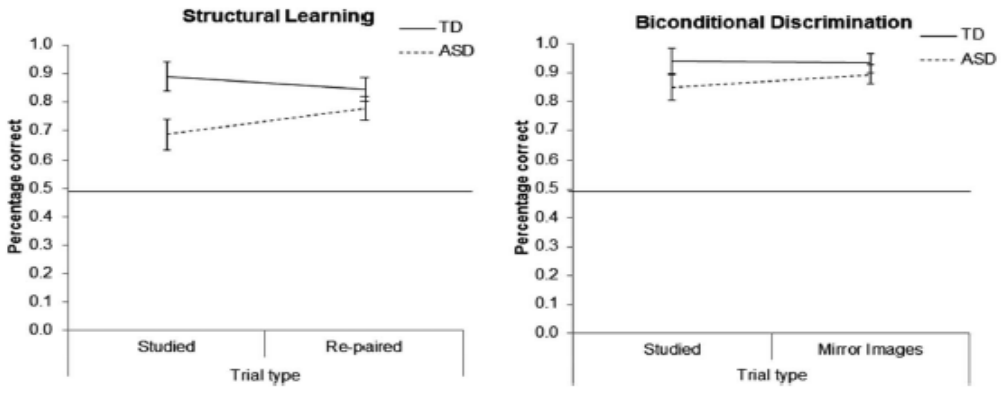



***Test***

Ratio scores (re-paired/(re-paired + studied)) were calculated to assess the two groups' difference between studied and re-paired trials (Figure 4). The ASD ($M$ = 0.55, $SD$ = 0.07) compared to the TD ($M$ = 0.48, $SD$ = 0.03) group showed a significantly higher ratio

score, $t(36) = 3.42$, $p < .01$, Cohen's $d = 1.11$, 95 % CI(0.40, 1.77) resulting from better performance on re-paired as opposed to studied trials. Directly comparing participants performance on re-paired and originally studied trials using a 2 (Group [ASD, TD]) x 2 (Trial type [studied, re-paired]) repeated measures ANOVA revealed a significant main effect of *Group*, $F(1,36) = 4.71$, $p < .05$, Cohen's $d = 0.70$, 95 % CI(0.03, 1.34), with higher performance for the TD ($M = 0.87$, $SD = 0.19$) compared to the ASD group ($M = 0.73$, $SD = 0.19$). A significant *Group x Trial type* interaction, $F(1,36) = 10.49$, $p < .01$, $\eta_p^2 = .23$, showed that TD participants only performed better on studied pairs ($M_{TD} = 0.89$, $SD_{TD} = 0.15$; $M_{ASD} = 0.69$, $SD_{ASD} = 0.28$), $p < .01$, Cohen's $d = 0.92$, 95 % CI(0.23, 1.57), but not re-paired trials ($M_{TD} = 0.85$, $SD_{TD} = 0.19$; $M_{ASD} = 0.78$, $SD_{ASD} = 0.18$), $p = .26$, Cohen's $d = 0.36$, 95 % CI(-0.28, 1.00), because the ASD group performed significantly better in re-paired compared to studied pairs, $p < .01$, Cohen's $d = 0.45$, 95 % CI(-0.20, 1.09). The main effect of Trial type was not significant, $F(1,36) = 1.24$, $p = .27$, Cohen's $d = 0.12$, 95 % CI(-0.34, 0.56).

Figure 4. *Accuracy as percentage correct for studied and re-paired test trials in Block 5 for Structural Learning (left) and for studied and mirror images in Block 5 for Biconditional Discrimination (right) for ASD and TD individuals. The horizontal line indicates chance performance. The data are presented as mean ± SEM.*



***Relation to social deficits in ASD***

A bivariate correlation analysis across the combined sample of ASD and TD participants showed a significant positive correlation between ratio scores and AQ scores (r = .43, $p < .01$), which was primarily due to an inverse association between performance on studied pairs and AQ (r = -.36, $p < .05$) rather than repaired trials and AQ (r = -.16, $p = .33$). At a subscale level, significant positive correlations were found between ratio scores and the AQ subscales Social Interaction (r = .37, $p < .05$), Attention Switching (r = .55, $p < .001$), and Communication (r = .42, $p < .05$) that again reflected inverse associations with performance on studied (Social Interaction: r = -.37, $p < .05$; Attention Switching: r = -.43, $p < .01$; Communication: r = -.31 $p = .06$) rather than repaired trials. Thus greater difficulties in acquiring structural discriminations were associated with higher self-reported autistic-like traits, especially in the social-communication and attention switching domains.

***Relation to executive functions***

Having established that there were no between-group differences in the CTT2 (Table 1), bivariate correlation analysis across the combined sample of ASD and TD participants showed significant negative correlations between CTT2 errors and performance on studied (r = -.43, $p < .01$; TD: r = -.46, $p < .05$; ASD: r = -.51, $p < .05$) and re-paired trials (r = -.44, $p < .01$ ; TD: r = -.51, $p < .05$; ASD: r = -.39, $p < .1$) of Block 5 of Structural Learning, indicating the more errors participants in both groups made on the CTT2, the worse their Structural Learning was. ANCOVAs analysing Structural Learning performance, with CTT2 as a covariate, however, left the pattern of results reported above unchanged. In particular, the main effect of group remained significant, $F(1,35) = 8.81$, $p < .01$, $\eta_p^2 = .20$, as did the associations between ratio scores and AQ total (r = .42, $p < .05$), Social Interaction (r = .36, $p < .05$), Attention Switching (r = .54, $p < .01$) and Communication (r = .43, $p < .05$) scores.

## Biconditional Discrimination

### *Learning*

Analysis of the percentage correct learning data in Figure 3 showed a marginal main effect of Block, $F(2.74,98.64) = 2.71$, $p = .05$, $\eta_p^2 = .07$, GGC, that was characterised by a significant quadratic trend ($F(1,36) = 7.19$, $p < .05$, $\eta_p^2 = .17$) due to non-significant decreases in performance over Blocks 1 – 3, followed by a significant increase to Block 4 ($p < .05$). There was no main effect of Group or Block x Group interaction, $F_{max} < 1.20$, $p_{min} > .29$, $\eta_p^2{}_{max} < .04$. Numbers of individuals needing three attempts or not reaching criterion at a certain block are presented in Table 2.

### *Test*

Ratio scores (mirror images/(mirror images + studied)) were calculated to assess the two groups' difference between studied and mirror image trials. Although the groups did not differ significantly in their ratio scores ($M_{ASD} = 0.52$, $SD_{ASD} = 0.06$; $M_{TD} = 0.50$, $SD_{TD} = 0.02$), $t(36) = 1.69$, $p = .11$, Cohen's $d = 0.55$, 95 % CI(-0.11, 1.18), direct comparison of the groups' performance on mirror image and studied trials using a 2 (Group [ASD, TD]) x 2 (Trial type [mirror image, studied]) repeated measures ANOVA showed a marginal *Group x Trial type* interaction, $F(1,36) = 3.17$, $p = .08$, $\eta_p^2 = .08$, with the ASD group performing better on mirror image ($M = 0.89$, $SD = 0.17$) compared to initially studied stimuli ($M = 0.85$, $SD = 0.25$), $p < .05$, Cohens $d = 0.26$, 95 % CI(-0.38, 0.90). No main effects were significant, $F_{max} < 1.65$, $p_{min} > .20$, Cohen's $d_{max} < 0.12$, 95 % $CI_{max}$(-0.34, 0.56), (see Figure 4).

## Transverse Patterning

### *Learning*

Analysis of the data from Figure 3 revealed a significant main effect of Block, $F(2.73,98.31) = 7.21$, $p < .001$, $\eta_p^2 = .17$, GGC, that was again characterised by a significant quadratic trend ($F(1,36) = 19.23$, $p < .001$, $\eta_p^2 = .35$) due to significant decreases in performance over Blocks 1 – 3 ($p < .05$) but no further significant changes in performance thereafter. There was no main effect of Group or Block x Group interaction, $F_{max} < 0.88$, $p_{min} > .44$, $\eta_p^2{}_{max} < .03$. Numbers of individuals needing three attempts or not reaching criterion at a certain block are presented in Table 2.

**Discussion**

The aim of this study was to examine the functional integrity of a hippocampal process known as *Structural Learning* in ASD that could play a critical role in the aetiology of the disorder because of its wide reaching involvement in many functional domains (Rubin et al., 2014). By adapting a paradigm from the non-human animal learning literature, it was possible to examine Structural Learning as well as other forms of configural learning that pose very similar processing requirements and that need minimal verbal instructions. Although all tasks involved simultaneous discriminations of simple geometric shapes, participants needed to take spatial arrangements into account only in Structural Learning. The current study, therefore, is a relatively direct behavioural test of hippocampal function in ASD.

We predicted lower learning performance for the ASD group only in *Structural Learning*. Moreover, we predicted that this lower performance would not be attributable to difficulties in executive functions, which would have implicated abnormalities in frontal-hippocampal interactions (Sanderson et al., 2006). These predictions were confirmed by the significantly lower performance in ASD compared to TD individuals over the five blocks of *Structural Learning* that could not be explained by executive functions or the ability to learn

simple discriminations. In addition, ASD participants who took part in *Biconditional Discrimination* or *Transverse Patterning* performed as well as TD individuals, suggesting that difficulties with Structural Learning result from the unique requirement to process the specific structural arrangement of stimuli rather than simply to bind two elements of a stimulus or to represent the rules common to all tasks. In the context of animal lesion studies, which demonstrate selective impairments in Structural Learning following hippocampal lesions (Sanderson et al., 2006), our findings lend support to the long-held view that atypical hippocampal function plays an important role in the aetiology of ASD (Bowler et al., 2011; Cooper et al., 2017; DeLong, 1992; Gaigg et al., 2015). This view is further supported by the significant associations between Structural Learning difficulties and self-reported autistic-like traits as measured by the AQ, especially in the domains of social interaction, communication (core autism features) and attention switching. Finally, the performance of participants who completed the Biconditional Discrimination task also pointed to Structural Learning difficulties in ASD. Here we expected ASD individuals to demonstrate better performance on mirror image compared to studied images because Sanderson et al., (2006) had shown that the automatic engagement of Structural Learning normally hinders performance on mirror image stimuli. Although not apparent in a ratio score, this pattern was confirmed by a trend for higher performance on mirror images compared to studied trials for ASD but not TD participants. Taken together, therefore, the findings reported here point relatively strongly to the possibility of altered hippocampal functioning in ASD and provide solid empirical foundations for further investigations of the relation between performance on Structural Learning tasks and structural or functional changes in the hippocampus in this disorder.

It has previously been shown that individuals with ASD have difficulties transferring information from one context to another (Plaisted et al., 1998; Swettenham, 1996). In light of this, one may wonder why ASD individuals were relatively unimpaired in their performance

on re-paired compared to studied trials in the Structural Learning task. A possible explanation is the fact that on each re-paired trial there are two possible routes to a correct answer instead of just one in the studied trials because information from two previously studied trials is crossed. For example, to perform well on a studied trial such as *black/white* vs. *white/black* (Figure 1 Column I Row A), the participant needs to know which configuration is correct, i.e. that black needs to be on the left side of white. However, to make the correct choice on a re-paired trial such as *black/white* vs. *striped/white* (Figure 1 Column I Row D), the participant may either remember that *black/white* rather than *white/black* (Figure 1 Column I Row A) is correct, or they may remember that *white/striped* rather than *striped/white* is correct (Figure 1 Column I Row B). Via such a strategy ASD individuals would have been able to increase their performance to above 2/3 of the trials.

Another feature of the current observations that may seem surprising when looking at Table 2 is that several individuals in both groups did not learn to criterion whereas the rats with hippocampal lesions in Sanderson et al., (2006) acquired three discriminations successfully. It is important to keep in mind, in this context, that the testing procedures for rats are in many ways quite different from those used here. Rats undergo pre- and postoperative testing, which is not possible in humans. In addition, rats are usually trained in several sessions over several days whereas the humans in the current study took part in one experimental session lasting about 30 minutes. It is possible that human participants may simply need more learning opportunities to acquire Structural Learning. This could be tested in a future study. In the current study, it is important to note that the overall performance of both groups was well above chance on the tasks suggesting that the adapted paradigm, overall, was of suitable difficulty. The question also arises as to whether ASD individuals are able to successfully perform Structural Learning at all. Inspection of performance on Block 4 of Structural Learning shows that the ASD participants solved only two out of the three

presented discriminations in the task at a level that was above chance indicating that they had not acquired Structural Learning but rather that they used extra-hippocampal strategies (e.g., intact Transverse Patterning) for the task.

It may also seem surprising that Sanderson and colleagues` rats showed better performance on Structural Learning compared to Transverse Patterning (Sanderson et al., 2006), whereas the opposite pattern was found in the human participants in the current study. It is possible that the difference in rat performance may be an artefact caused by a between-subjects design and differences in cognitive abilities in different rat populations since the rats performing Structural Learning also performed better in the Simple Discrimination task. This suggests that the rats performing Transverse Patterning may have had initial difficulties discriminating two simple geometric shapes. The current study has the advantage that, despite being a between-subjects design, all groups were matched on cognitive ability, age, and gender, thus making comparison of task difficulty easier.

It is also possible to argue that the Structural Learning task was the most complex of the three and that because of their difficulties with complex information processing (Minshew & Goldstein, 1998), this task might have been more difficult for the ASD participants. However, there is a danger of circularity in assuming a task is complex simply because ASD participants find it difficult. An alternative explanation is in terms of relational binding (Bowler et al., 2011), which posits particular difficulties in ASD with forming relations between items and their contexts. Bowler et al. (2011) cite Halford's (1992) *taxonomy of cognitive development* to define the relational processing requirements of any given task by defining the number of items and relations and the type of relations. Of particular relevance to ASD is Halford's notion of *ternary relations* - the processing of relations among triplets of items, which the Structural Learning task can be interpreted as requiring. On this analysis, the present findings reveal an ASD-related difficulty with forming ternary relations. Although

relational binding and by implication the capacity to process ternary relations has been shown to be specifically related to the hippocampus (Opitz, 2010), further research is needed to confirm the hippocampal-dependent nature of levels of relational complexity.

Further, there is a possibility that ASD individuals in the current study were affected by atypical parietal lobe functioning. Behavioural similarities in ASD and parietal patients in the areas of memory (Adlam et al., 2009; Berryhill et al., 2010; Davidson et al., 2008; Drowos et al., 2010) and attention (Behrmann et al., 2004; Han et al., 2004; Malhotra et al., 2009) have led to the parietal lobes being advocated as contributors to the observed behavioural difficulties in ASD (Boucher and Mayes, 2012; Maister et al., 2013). In addition, rats with hippocampal and parietal lesions showed close to chance structural learning (Aggleton et al., 2007; Sanderson, 2005). Finally, the correlations reported in the current study suggest that good attentional shifting skills may have benefitted participants' performance in Structural Learning.

The current findings also have important implications for future research and remediation for persons with ASD. The findings can help to identify the kinds of situations that are taxing for persons with ASD and which could be taken into consideration when designing daily life environments. For example activities such as learning to navigate new environments, trying to remember where they met a person and what their name was, or trying to predict an outcome of a situation depending on the context can all involve Structural Learning. The design of remediation programmes should aim to draw on an understanding of the strengths of persons with ASD to alleviate their difficulties in a manner similar to that used in amnesia research. For instance, individuals with hippocampal amnesia have been found capable of performing scene construction relying on their intact semantic memory (Mullally et al., 2014). In a similar vein, ASD individuals may be able to draw on preserved semantic memory and detailed focused perceptual styles to acquire Structural Learning in

real-life situations. Finally, further studies should examine whether a Structural Learning deficit in ASD extends to the temporal domain (Aggleton et al., 2007), as studies showing difficulties remembering the temporal order of item presentation (Bigham et al., 2010; Ni Chuileann and Quigley, 2013; Poirier et al., 2011; Ring et al., 2016) would suggest.

There are some limitations to the current study. The results may have been compromised by a ceiling effect in the TD group. However, this seems unlikely since there were participants who needed three attempts or did not reach criterion on a particular block. The sample size may be considered relatively small and together with the use of a between-subjects design, it was not possible to examine performance across experimental tasks in the same participant. However, the design choice used here seemed more appropriate to avoid transfer and interference effects caused by the similarity of the procedures and materials used in the three tasks. A further limitation is that it was not possible to administer the ADOS to all participants to corroborate their clinical diagnosis and formally characterise their clinical presentation using this standardised measure. Finally, a number of ASD participants in the current sample reported prescriptions for psychotropic medication (primarily antidepressants), which is to be expected given the high co-morbidity of ASD with other psychiatric disorders (Buck et al., 2014). Although this may affect the results, these participants were relatively evenly distributed across the three experimental conditions, thus mitigating this potential confound. Future studies, should, however, consider using medication washout procedures to reduce the impact of medication or, preferably, recruit sufficiently large samples to formally examine the role of medication and co-morbidity on the findings.

Perhaps the greatest advantage of the paradigm presented here is that because it is a direct human adaptation of a non-human animal paradigm, it enables us to speculate about possible brain regions underlying the behavioural difficulties observed in ASD. It also has

potential utility for the use in less verbal or non-verbal individuals and as such makes possible the testing of severely disabled as well as very young individuals with ASD, who currently are an under-researched population and one for which it has been very difficult to find suitable test procedures. Overall the data presented here suggest specific difficulties in Structural Learning in ASD that are likely to form the basis of more complex processes such as spatial navigation, episodic memory and the competencies necessary for successful social interactions. The findings further underpin the idea that ASD is not characterised solely by difficulties in social cognition but by more domain-general cognitive difficulties.

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