Utilizing Neural Gain as a Model for Explaining Features of Autism Spectrum Disorders: The effects of constitutive locus coeruleus activity on attention-based learning

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HONOR PLEDGE

I pledge my honor that this paper represents my own work in accordance with University regulations.

/s/ Michael Granovetter

Acknowledgements

Two years ago, I had a conversation after class with Professor Yael Niv about my interests in autism research and the work in her lab, a discussion that would ultimately evolve into the thesis on the following pages. While at the time I appreciated how Professor Niv took the initiative to meet with her students over coffee after each lecture, I was soon to learn that this level of engagement is reflected in every aspect of her work as a teacher and mentor. Professor Niv has been an ideal advisor, always being available to offer insightful commentary and guidance on my research, while at the same time allowing me enough independence to pursue and confront the scientific questions that have interested me the most. I cannot be thankful enough for the amount of advice, support, and encouragement Professor Niv has provided me from the moment I joined the lab.

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My interest in understanding the basis of autism stems from my admiration and pride of my brother Jonathan’s tremendous development into an independent and articulate adult who has defied every obstacle that his autism diagnosis has required him to confront throughout his childhood. His perpetual drive to improve each day has always been a quality I have regarded and has been a source of motivation for me. As a demonstration of his kind and patient nature, Jonathan helped to pilot an early version of my thesis experiment, and over the course of several hours, provided me with crucial input that allowed me to optimize the final study design. I would like to dedicate this thesis to Jonathan, my sister Madeleine, and my parents, for their unconditional care and support, before, now, and always.

Abstract

The goal of this thesis is to investigate the interaction between breadth of attention and trial and error learning in individuals with autism spectrum disorders. Previous literature suggests that autistic individuals attend to and consequently learn from environmental stimuli in an atypical manner, although these studies have principally relied on measuring attentional focus using coordinate measurements from eye tracking and have generated conflicting results without elucidating a unified mechanism to explain autistic individuals' attention and learning difficulties. Here we suggest a model for understanding some features of learning in autistic individuals that is based on neural gain. Specifically, previous work has shown that neurotypical individuals with high neural gain (a state associated with increased norepinephrine release, which can be assessed non-invasively using pupillometry) attend to and learn more readily from those stimulus dimensions to which they are predisposed to. In contrast, when in a state of low gain (a condition associated with down-regulated norepinephrine release), neurotypical individuals can integrate information and learn about multiple stimulus dimensions. On the basis of literature suggesting that autistic individuals' significantly elevated baseline pupil sizes might be a consequence of increased norepinephrine production, we hypothesized that autistic individuals are constitutively in a state of high gain. We tested this hypothesis by comparing the performance and pupillary responses of autistic and neurotypical teenagers and young adults engaged in trial and error learning in a multidimensional environment. Contrary to our hypothesis, autistic individuals learned equally (but not efficiently) about multiple stimulus dimensions (and notably from both social and nonsocial stimuli), although their pupillary responses indeed suggested higher levels of norepinephrine. We therefore consider how the chronic release of norepinephrine that is typically implicated in autistic individuals might ultimately induce a significant decrease in gain, thereby providing a possible neural-based explanation for autistic individuals' deficiencies at efficiently learning from environmental cues.

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Chapter 1

Introduction

Some material in this chapter was adapted from Granovetter (2014).

1.1. Autism Spectrum Disorders

Approximately 1 in 68 children in the United States is diagnosed with autism spectrum disorders (ASDs; Baio, 2014), described in the *Diagnostic and Statistical Manual of Mental Disorders* as a condition in which one experiences disproportionate anxiety as a consequence of hyper-sensitivity to environmental stimuli and change (American Psychiatric Association, 2013). In addition, about 45% of autistic children exhibit an intellectual disability, and social development and communication is often compromised in these individuals (Lai, Lombardo, & Baron-Cohen, 2014). A range of personalized interventions are available for individuals with the disorder, and while behavioral and therapeutic treatment plans can improve several debilitating autistic characteristics, many deficits (in particular, with respect to social communication abilities) remain (Granovetter, 2013a; Lai et al., 2014). Psychosocial interventions are incapable of permanently amending the neurological problems associated with autism, and medications for the disorder can induce a variety of side effects, including but not limited to weight gain, fatigue, extrapyramidal symptoms, and seizures. There is thus an urgent need to better understand the neural basis of the disorder, so as to accelerate patients' initial diagnosis (Lai et al., 2014) and to offer better-targeted treatment interventions in the clinic (Granovetter, 2013b).

The basis of ASD certainly eluded families and healthcare providers many decades before the clinician Eugen Bleuler gave the condition a name in 1911 (Blatt, 2014) and Leo Kanner outlined its first standardized diagnostic criteria in 1943 (Baker, 2013). However,

perhaps these practitioners initiated a research trajectory focused on a limited scope of features, given "autism's" derivation from the Greek word "autos," meaning self. In retrospect, while historians realized that Bleuler's "autistic" patients were for the most part schizophrenic, the term referring to inner withdrawal remains in use to this day (Blatt, 2014). Even in the years after Kanner, the public continued to believe in his proposal that the social deficiency seen in autistic children was a product of poor parenting and innate inclinations ("History of Autism Blame," 2002), and while this idea is readily rejected today, clinicians and researchers alike continue to disagree on the causes of social impediments in autistic individuals.

Thus, one goal has been to determine whether areas of the brain associated with social behaviors differ in terms of their anatomy and resting-state activity in autistic individuals, as compared with members of a neurotypical population. Findings show that individuals with an ASD do appear to exhibit excessive neural activity in regions such as the medial prefrontal cortex (PFC; an area associated with self-referential thought; Tamir & Mitchell, 2012), the superior temporal sulcus (an area associated with the recognition of human movements), the temporo-parietal junction (TPJ; an area associated with theory of mind), the amygdala (an area associated with fear processing), and the fusiform gyrus (an area associated with facial recognition; Lai et al., 2014; Purves et al., 2013). Findings from diffusion tensor imaging suggest that social deficiencies observed in autistic children might be a collective product of atypical white matter connections in areas of the cortex near and including the PFC and TPJ (Barnea-Goraly et al., 2004). Furthermore, some researchers claim to have revealed a significant absence of activity in autistic individuals' mirror neuron circuits—networks that respond equally to select actions and emotions performed by either the self or a conspecific—again suggesting that autism

might develop as a result of abnormalities in neural systems delegated to processes such as social cognition and empathy (Oberman et al., 2005).

However, social deficits constitute only one of the many features of ASD, and the aforementioned hypotheses might not appropriately address other hallmark symptoms of the disorder, most notably disparities in attention-based learning. Attentional deficiency is a commonly documented autistic feature, given that 28-48% of individuals with an ASD also have an Attention-Deficit Hyperactivity Disorder diagnosis (Lai et al., 2014). The true neural mechanism underlying the behavioral features of autism must therefore take into account the gamut of qualities associated with the condition, and probing autistic individuals' attentional and learning deficits is a course that might reveal a cohesive explanation of the disorder, given attention's range of effects on cognitive behaviors. As pupil gaze, response, and size might together provide critical intuition into neural models for cognitive functioning, investigators have thereby moved to reflect upon how such variables might specifically offer a unified explanation of autistic individuals' distinctive manner of engagement with their surroundings.

1.2. Saccades as a Parameter of Attention in Autistic Individuals

Pupil gaze has recently garnered consideration as a possible diagnostic criterion for identifying autism in infants, and so research initiatives have aimed to distinguish patterns in pupil gazes and saccades between autistic and neurotypical children. One investigation demonstrated that toddlers who went on to develop autism exhibited abnormal visual attentional processing, and more specifically, fixated their gazes on select environmental stimuli before disengaging to another object in the visual field (Elsabbagh et al., 2013). Moreover, Landry and Bryson (2004) reported that autistic participants remained fixated on stimuli for significantly longer durations than both Down syndrome and neurotypical controls. Landry and Bryson's

results might thus support the idea that an autistic individual's cognitive development is hindered by what Bryson et al. (2004) refer to as "sticky" attention. That is, individuals with autism seem to limit exploration of objects in their environment: their attention stays "stuck," or fixated, on one particular stimulus at a time (Bryson et al., 2004). However, some attempts to replicate Landry and Bryson's (2004) work have been unable to identify such differences in disengagement capabilities between autistic and control participants (Fischer, Koldewyn, Jiang, & Kanwisher, 2013), and so while autistic individuals clearly have attentional abnormalities, the mechanism by which these deficiencies in attention foster has yet to be consistently demonstrated.

Others have proposed that differences in saccadic movements in autistic children might explain their relatively regressive social development. In one prospective longitudinal study, Jones and Klin (2013) identified a critical period when infants that went on to develop autism less frequently fixated their gazes on others' eyes than age-matched participants that did not go on to develop the disorder. Moreover, Dalton et al. (2005) found a significant positive correlation between the time in which autistic participants' eyes were fixated on the eyes of presented faces, and blood oxygenated level dependent (BOLD) activation in the fusiform gyrus, which is associated with face processing, and the amygdala, which is involved in emotional processing. Together, these findings suggest the possibility that social deficiencies in autistic individuals could in fact be consequences of autistic individuals' incapacity to selectively attend to social stimuli—including the eyes of conspecifics—during a developmental critical period, thus deterring long-term learning of social cues and resulting in a permanent aversion to social stimuli.

That being said, while the work of Jones and Klin (2013) and Dalton et al. (2005) offer support for the idea that social impairments in autistic individuals are based on inborn deficiencies of attention, other behavioral research has shown that such an attentional deficit is not necessarily exclusive to the processing of social stimuli. For example, one investigation showed that autistic children display signs of "sticky" attention regardless of whether environmental stimuli are social or non-social in nature (Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008). Moreover, research has yet to demonstrate whether autistic individuals' apparent decline in engagement to social stimuli parallels or is fundamentally different from their decline in engagement to nonsocial stimuli. Thus, collectively, the literature suggests that autism might not be a consequence of a natural-born deficit to cortical areas such as the TPJ or amygdala as was previously posited (Baron-Cohen et al., 2000; Lombardo, Chakrabarti, Bullmore, MRC AIMS Consortium, & Baron-Cohen, 2011), as it is possible that autistic individuals might equally engage with novel social and nonsocial stimuli. Instead, it is more probable that such areas do not sufficiently develop due to autistic individuals' inherent attentional aberrations, a potential alternative explanation of the social deficits associated with autism that remains to be tested.

Furthermore, the question persists as to why individuals with autism exhibit an initial aversion to some stimuli and a preference for others, and what processes might guide such predispositions. A setback to using pupil gaze fixation as a measurement of attention is that this method can only reveal where an individual shifts his visual field during any given period of time, but not what particular components of stimuli individuals are attending to, processing, and learning from in such a way as to guide future eye movements. One possibility is that saccades are not a measure of general attention, but rather are indicators of an individual's reward

preferences. In fact, the mesolimbic system (a circuit that regulates reward-based learning) is known to actively modulate saccades (Basso & Sommer, 2011), and saccades to stimuli of greater reward value are typically faster (Chen, Chen, Zhou, & Mustain, 2014). In light of this, one might suggest that a lack of engagement with a select environmental stimulus (as determined by saccadic movements) implies that the stimulus in question has been ascribed a relatively low reward value by the viewer. As the association of reward values with stimuli is typically a product of prior experience (Daw & Doya, 2006), the question emerges as to what might cause an individual with autism to fail to appropriately gain the necessary prior experience to learn from features of typically rewarding social stimuli—say, for example, the eyes of a parent. Thus, eye movements themselves might not provide adequate information to expose the specific features of stimuli that individuals with autism attend to during attention-based learning. Perhaps then, studying other neural substrates for attention is called for, to complement previously utilized behavioral measurements probing attentional differences in autistic individuals.

1.3. Neural Gain: A Model for Locus Coeruleus Activity

Norepinephrine (NE) might be an appropriate physiological marker for studying attention in individuals with autism: although traditionally the neuromodulator is cited for its ability to monitor arousal and reward states (Aston-Jones & Cohen, 2005), the molecule might also be involved in the regulation of attention and learning (Eldar, Cohen, & Niv, 2013a). Before we consider NE's potential contribution to autistic features, we will first discuss NE's effects on neural circuitry and consequent attention-based behaviors in neurotypical populations.

NE is primarily released to the cerebrum, hippocampus, and cerebellum, in response to activation of a relatively small population of noradrenergic neurons in the dorsolateral pons, known as the locus coeruleus (LC). NE modulates the activity of both excitatory and inhibitory

neurons, thereby regulating the excitatory/inhibitory balance that occurs in a gamut of neural circuits, given the broad range of regions that are innervated by the LC (Figure 1.1). At the same time, a significant proportion of LC projections are to cortical regions involved in attentional function, which justifies the idea that the LC might serve as a brain-wide modulator of attention (Aston-Jones & Cohen, 2005).

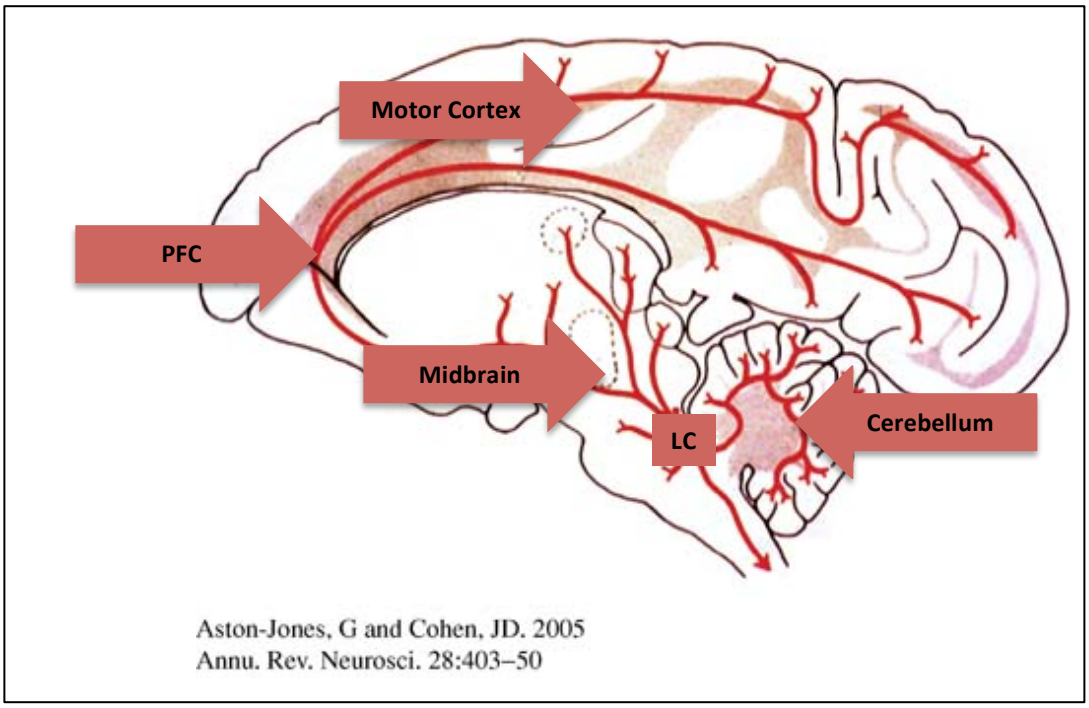


Figure 1.1. Sagittal cross-section illustration of a non-human primate brain, showing the range of LC projections to assorted cortical and subcortical regions. The gamut of areas innervated by LC suggests that the LC's role in regulating excitatory/inhibitory homeostatic balance can have a variety of effects on behavior. It should be noted that a majority of projections are made to the frontal and parietal cortices, regions that often play a critical role in the regulation of attention. Figure adapted from Aston-Jones & Cohen (2005), also based on Bear, Connors, & Paradiso (2007), and Butler & Hodos (1996).

Neural gain is associated with LC activity, and by consequence, global NE production in the brain, which modulates neurons' susceptibility to activation (Aston-Jones & Cohen, 2005). The probability of the activation of a neuron is a function of the input to that neuron and the present gain state (Eldar et al., 2013a; Servan-Schreiber, Printz, & Cohen, 1990):

$$Activation = \frac{1}{1+e^{-(gain*net\ input)}} \quad \text{(Equation 1.1)}$$

An increase in gain amplifies the effects of both excitatory and inhibitory inputs to a neuron, and as a result should elevate an individual neuron's signal-to-noise ratio, regardless of the initial input. Conversely, a decrease in gain should decrease said ratio (Servan-Schreiber et al., 1990). Applying this idea to an entire neural population suggests that neural gain can be thought of as a way to adjust overall signaling strength in neural pathways. When neural gain is high, there is an increased probability that excitatory neurons will be excited and inhibitory neurons will be inhibited, but when neural gain is low, the relative strength of inputs' effect on respective output is more unpredictable given the consequent decrease in the signal-to-noise ratio of individual neurons (Aston-Jones & Cohen, 2005; Servan-Schreiber, et al., 1990). Thus, the release of NE from the LC might serve to simultaneously amplify excitatory pathways and dampen inhibitory pathways, globally throughout the brain. (Figure 1.2; Aston-Jones & Cohen, 2005).

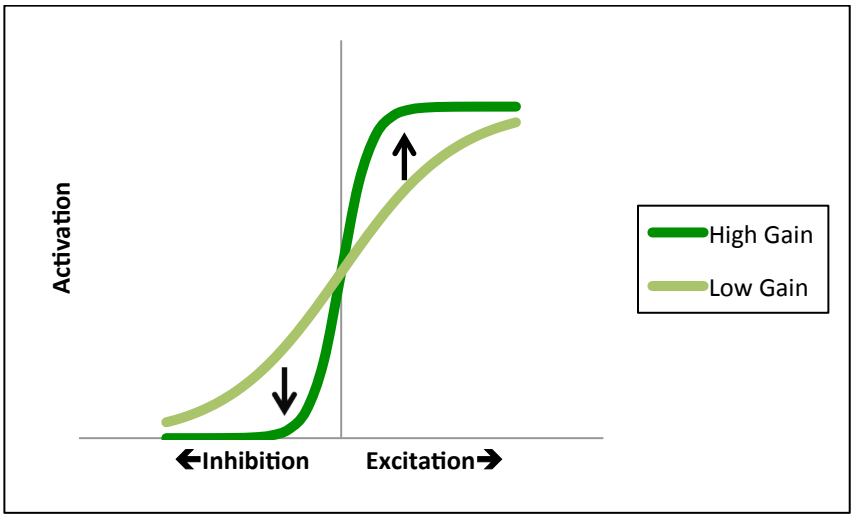


Figure 1.2. The effect of neural gain on neural activation. Increasing gain increases the effects of neural input on neural output. Figure adapted from Aston-Jones & Cohen (2005), also based on Eldar et al. (2013a).

1.4. Neural Gain's Effects on Behavior, Attention, and Learning

Given the LC's location in the pons (Samuels & Szabadi, 2008), it is difficult to study this region's functional activity without the use of invasive techniques. However, work in non-human primates has established associations between pupil size, NE output from the LC, and attentional behaviors (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994). That is, during "tonic" LC activity—marked by hyperactive LC baseline firing and associated with increased NE release from the LC—there appears to be a significant decrease in performance on attention-based tasks. In contrast, "phasic" activity—marked by hypoactive LC baseline firing with infrequent transient bursts of LC responsiveness and associated with decreased NE release from the LC—there appears to be a significant increase in performance on attention-based tasks. Moreover, a parallel association between LC-NE system activity and task engagement has been documented in humans. Increased baseline pupil sizes and depressed pupillary responses (in other words, relatively small pupil dilations) can be measured during task disengagement, and decreased baseline pupil sizes and elevated pupillary responses can be measured during increased task engagement (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010). These results demonstrate that pupillometry might be an effective non-invasive practice to infer the extent of noradrenergic output from the human LC and deduce the LC's effects on engagement.

Moreover, recent research shows that neural gain can additionally influence the way in which individuals focus their attention on different dimensions of environmental stimuli. Eldar et al. (2013a) hypothesized, on the basis of neural network simulations, that when gain is high, neural activity should be localized and "clustered" (Eldar et al., 2013a), whereas when gain is low, neural activity should extend globally. In Eldar et al.'s (2013a) investigation, participants initially answered questions from the Index of Learning Styles (ILS) questionnaire, a survey that

informed the researchers as to whether each participant was predisposed towards semantic-based or visual-based learning when interacting with the environment. Participants were then presented with pairs of stimuli, and they selected one of the two options in order to obtain a monetary reward for each trial. The stimuli were categorized on the basis of semantic features (e.g., food products versus office items) and on the basis of visual features (e.g., gray-scale versus color). Both semantic and visual categories were associated with reward values, with one semantic and one visual feature being more rewarding than the other on each particular block of trials. For instance, in one block, participants needed to learn that office items offered more reward than food products, and that gray-scale items offered more reward than those in color. By correlating performance on this multidimensional learning task with pupillometry measurements, Eldar et al. (2013a) demonstrated that with increased gain, there was a strong correlation between the stimulus dimension that individuals learned about and the stimulus dimension that individuals were predisposed to utilize for learning. In contrast, when gain was low, there was no such correlation between what individuals learned and their prior individual predispositions for learning. Therefore, in general, one can shift from a dominant style of learning to another that might be less familiar to that individual, especially when in a state of lower gain (Eldar et al., 2013a).

1.5. The Relevance of Neural Gain for Understanding Autism

The above literature review outlining the connections between NE, neural gain, and attention demonstrates pupillometry's potential utility in autism research, in order to clarify the mechanism underlying autistic individuals' abnormalities of attention. Given autistic individuals' attentional deficits (Lai et al., 2014), researchers have indeed previously interrogated whether NE modulation differs in individuals with autism compared with members of a neurotypical

population (Cook, 1990). Indeed, individuals diagnosed with ASD have significantly higher baseline pupil sizes than neurotypical controls (Anderson & Colombo, 2009), and likewise, autistic individuals generate significantly lower concentrations of salivary alpha-amylase (a digestive enzyme, which is most probably produced at a rate inversely correlated to that of NE) than individuals in an age-matched control population (Anderson, Colombo, & Unruh, 2013). These findings suggest that individuals with autism have elevated NE levels, in comparison with neurotypical individuals. In fact, LC activity undergoes changes during episodes of fever, and interestingly, autistic individuals show behavioral improvements under febrile conditions, which provides additional evidence for a possible association between the LC-NE system and autistic features (Mehler & Purpura, 2008).

Nevertheless, the question remains as to why elevated NE concentrations might result in an attentional deficiency, and not an attentional advantage (as might be expected, given that the high gain state allows one to focus attention on select stimulus features; Eldar et al. 2013a), in individuals with autism (Lai et al., 2014). In fact, the conclusions from pupillometry experiments conducted in neurotypical populations in many ways apparently contradict some findings investigating attentional capacity in autistic individuals. For example, contrary to Gilzenrat et al.'s (2010) demonstration that depressed pupillary responses (that is, tonic LC activity) are associated with task disengagement, autistic individuals (who have relatively large baseline pupil sizes, possibly indicative of tonic LC activity) find it difficult to disengage from select stimuli (Landry & Bryson, 2004). Nevertheless, it is uncertain whether in this case, autistic individuals have a disposition for *task*, as opposed to *stimulus*, engagement, given that distinctions between pupillary responses occurring during task engagement compared to stimulus engagement have

not been well studied. Regardless, it is possible that autistic individuals do not less frequently disengage than neurotypical individuals at all (Fischer et al., 2013).

Another possible explanation of the effect of chronic NE release on autistic individuals' attentional capacities is that autistic individuals might constitutively be in a state of high neural gain, given the correlation between elevated baseline pupil sizes and high gain (Eldar et al., 2013a). Notably, it is posited that individuals with high gain are more susceptible to priming on one dimension over the other (Eldar, Niv, & Cohen, 2013b). Perhaps then, if individuals with autism are constitutively in the high gain state, the first stimulus that they are presented with immediately becomes the stimulus that they prefer to attend to, in a way establishing a "predisposition" *ad hoc*. However, again, it is unclear whether chronic NE release would have such an effect, given that individuals with autism appear to show a hypersensitivity to multiple environmental stimuli, as opposed to heightened sensitivity to select stimulus features (Granovetter, 2013a).

In this thesis, we thereby seek to investigate whether autistic individuals are constitutively in a state of high neural gain, and whether in fact autistic individuals' attention-based learning behaviors are consistent with those expected in instances of high gain. Our hypothesis is guided by several aforementioned findings in the literature (Figure 1.3), most notably: (1) individuals with autism show patterns of "sticky" attention (Bryson et al., 2004) when processing visual stimuli (Bryson et al., 2004; Landry & Bryson, 2004), although this conclusion has been contested (Fischer et al., 2013); (2) autistic individuals exhibit larger baseline pupil sizes than neurotypical individuals (Anderson & Colombo, 2009); and (3) elevated baseline pupil sizes have been associated with the high neural gain state (Eldar et al., 2013a).

If autistic individuals are indeed more frequently in a state of high neural gain and rarely experience a significant decrease in gain, then this would lend evidence to the idea that they would be compromised in integrating multi-dimensional information from stimuli. In Eldar et al.'s (2013a) work, neurotypical individuals with high gain had a predilection to learn from stimulus dimensions that they were already predisposed to learn from. In contrast, integration of multiple stimulus dimensions (including those that participants were not predisposed to learn from) occurred most often when participants had low gain (Eldar et al., 2013a). Therefore, we conjecture that if autistic individuals are constitutively in a state of high gain, then they will be deficient at integrating information and learning from stimulus features that they are not already predisposed to utilize for learning. We tested this idea by comparing autistic and neurotypical individuals' respective performances on an experimental task adapted from Eldar et al. (2013a), while recording pupillometry measurements in these participants in order to approximate individual neural gain (Eldar et al., 2013a). In addition, by employing some stimuli that involve social features (e.g., facial expressions), we assessed whether attention-based learning differences in autistic individuals can be attributed to the social content of environmental stimuli. This latter measure was intended to determine whether deficits in social cognition in individuals with autism (Lai et al., 2014) are merely a consequence of innate differences in attention-based learning computations.

We predicted that autistic participants would be more likely to exhibit behavioral and physiological features associated with the high neural gain state than neurotypical participants, among whom we anticipated observing a range of behavioral and physiological features as seen in Eldar et al.'s (2013) study. Given that we expect neural gain modulations to influence a variety of circuits in the brain (Aston-Jones & Cohen, 2005), we also predicted that autistic

individuals' deficiencies in attention-based learning would not necessarily be specific to the social content of stimuli.

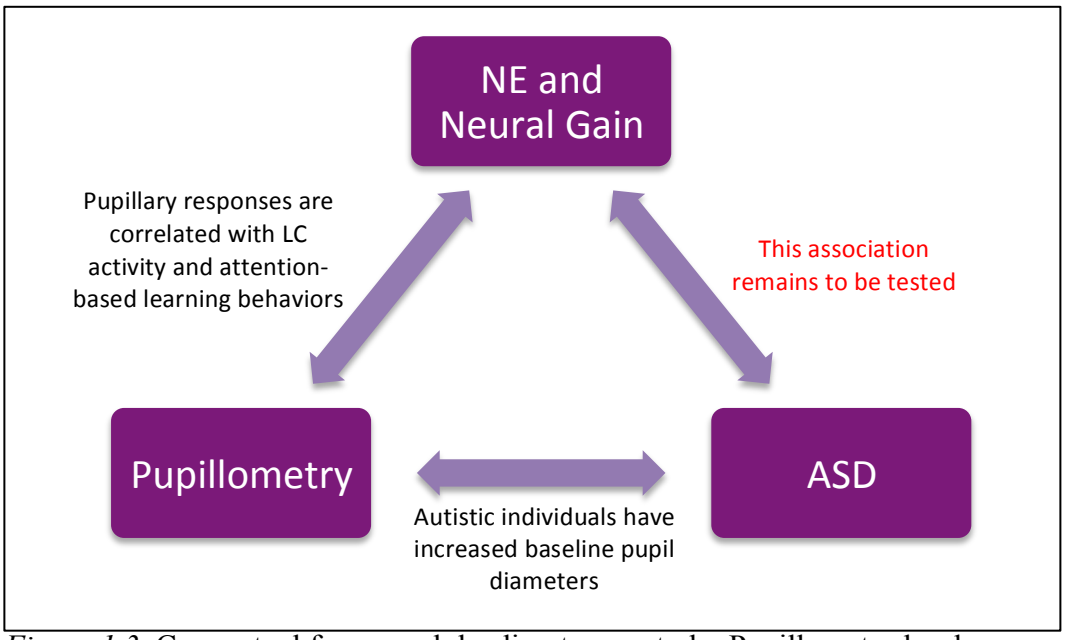


Figure 1.3. Conceptual framework leading to our study. Pupillometry has been used both as a test diagnostic criterion for ASD and as a vehicle for understanding attention-based learning. In our study, we correlate pupillometry to attentional and learning behaviors in autistic individuals to test for the missing link in this diagram.

Chapter 2

Methods

Some material in this chapter was adapted from Granovetter (2014).

2.1. Participants

Participants consisted of 22 males between the ages of 12 to 21 years enrolled in several New Jersey middle schools and high schools. 12 participants had a diagnosis of ASD, according to school administrators, and the remaining 10 were enrolled in a public school curriculum that assumes its students do not have a history of neurological, psychological, or psychiatric-related conditions that would interfere with functioning and performance on everyday tasks. Given the lack of availability of subjects with ASD, we used a wide age range during study recruitment in order to increase the potential sample size for this investigation. The age range employed allowed all middle and high school-aged individuals in a select number of schools specialized for autistic children to be eligible for participation. The upper bound criteria for age reflects the fact that many autistic individuals in special education high schools in the state of New Jersey receive their high school diploma at the age of 21 years on average. Furthermore, as ASD is most commonly diagnosed in males (Lai et al., 2014), we limited the study to males only.

Special education schools were chosen from a list of institutions complied by Autism New Jersey (Autism New Jersey, 2014), and the final selection of participating institutions—the Gramon Family of Schools and the Youth Consultation Service Sawtelle Learning Center—was decided on the basis of schools' respective availabilities and proportions of students who administrators classified as "high functioning" individuals with a diagnosis of ASD. Eligibility requirements were that participants could read at or beyond second-grade proficiency, and that

participants were capable of remaining seated for the 1-hour study duration. Whether individuals met these criteria was determined after consultation with schoolteachers and administrators.

We recruited all neurotypical participants from Glen Ridge High School, a New Jersey public high school located at a proximate distance from the other study sites. Control participants were selected by the institution's principal, on the basis of his knowledge of student availability, and were age-matched to autistic participants as best as possible in light of availability. We aimed to include approximately the same number of participants above and below the age of 16 years, in each participant group. We do not have the ages of 3 adult participants in the autistic group, thus we assumed their age was approximately 19.5 years, the mean of the age range of adults eligible for our study. Using this value, the mean ± standard error of the autistic participants was 15.96 ± 0.69 years, and that of the control participants was 15.70 ± 0.54 years. Thus, our groups are approximately matched on age.

Letters were sent to parents of all prospective participants, explaining the purpose and logistics of the investigation. For all participating minors, written informed parental consent was required in addition to assent from the participants, and for all participating adults, only written informed consent from the participant was required. All participants received a minimum compensation of $12 for the estimated 1-h session. Additionally, participants received an extra $0.04 per reward point that they received when completing the task, although no participant was allowed to accumulate more than $15 in compensation from reward points, based on the task design. All participants were orally debriefed about the purpose of the experiment at the end of their individual study sessions.

We ran all autistic participants who enrolled in the study by January 2015. While 12 autistic participants enlisted to take part in the investigation, only 10 completed the entire task.

Given that the 2 participants who did not sit for the complete length of the experiment also performed at or below chance (Section 3.1), we excluded these participants from the final analyses. As such, we ran 10 control participants, so that the number of participants in each group would be equivalent. An aide from the school was allowed in the testing room, in the case that school administrators made such a recommendation. No aide was allowed to provide interactive feedback to the participant throughout the study duration. The research was reviewed and approved by Princeton University's Institutional Review Board.

2.2. Stimuli

During the experimental task, participants were shown 18 sets of 24 stimuli each. Of these, 15 sets contained images, and 3 sets contained words. (We limited the number of stimulus sets containing words due to autistic participants' variable reading capabilities.) Four of the image sets and two word sets were adapted from Eldar et al. (2013a). The other word set was produced with the Processing programming environment (Reas & Fry, 2007). Two image sets were adapted from the Karolinska Directed Emotional Faces (Lundqvist, Flykt, & Öhman, 1998), one image set was adapted from the Center for Vital Longevity Face Database (Minear & Park, 2004), and one image set was adapted from the Face Place (Righi, Peissig, & Tarr, 2012; stimulus images courtesy of Michael J. Tarr, Center for the Neural Basis of Cognition and Department of Psychology, Carnegie Mellon University, http://www.tarrlab.org/; funding provided by NSF award 0339122). The remaining image sets consisted of images downloaded from different sources across the Internet that were found with Google Images. Images were edited using Adobe Photoshop CS6 (Adobe Systems), Adobe Fireworks CS6 (Adobe Systems), Microsoft Photo Editor for Windows XP (Microsoft), Microsoft Word 365 (Microsoft), and Picasa 3 (Google). In order to best ensure that pupillary responses were not a consequence of

differences in luminance across stimuli, all images were edited to be at nearly equal luminance, using the same software employed by Eldar et al. (2013a; Appendix B).

Participants viewed the stimuli on a Dell XPS laptop computer monitor, and the images were displayed using MATLAB R2014b (MathWorks) and The Psychophysics Toolbox (Brainard, 1997).

2.3. Task

The design of the experimental task for this study was adapted from Eldar et al. (2013a). Participants were first asked to complete a preselected sample of items from the Index of Learning Styles (ILS) questionnaire—questions that specifically pertained to the sensing-intuitive axis (Felder & Spurlin, 2005; Appendix A). This survey was used to determine whether each participant had a general predisposition for learning from either visual or semantic features of environmental stimuli. Questions were presented verbally to all participants to minimize effects of variability in reading proficiency across participants. The experimenter also pointed to each word of the questions and answer choices as they were read aloud, an effective approach for capturing the attention of autistic children (Akechi, Kikuchi, Tojo, Osanai, & Hasegawa, 2013). ILS scores were computed by assigning a value of 0 to (a) answer choices (those that describe sensing learning styles) and a value of 1 to (b) answer choices (those that describe intuitive learning styles; Felder & Spurlin, 2005; Appendix A). The values were summed and divided by the total number of questions to generate ILS scores for each participant between 0 and 1.

Participants were then shown the following instructions (with visual examples, as appropriate): “In the following games, you will be asked on each trial to choose between one of two options, one on the left or one on the right. The options may be images, or they may be words. You will use the left arrow key to choose the left option or the right arrow key to choose

the right option. After you pick an option, the number of points you get for it will show up above the item. The number of points that you could have gotten for the other option is also shown. You can receive two points, one point, or no points at all. For each point you get, you earn 4 cents. You will receive this money after the experiment. You will have 3 seconds to choose an option. Use your time to evaluate the items. But don't be late. After 3 seconds you will not be able to choose an item and get any points." Then, after a brief training period, participants were shown the following: "The number of points that you get for different options has a pattern. Some options will always give you more points, and some will give you less. Your job is to figure out what is the general rule that will determine how many points you will get. You will play 18 games. Each game will have a different rule to learn. Remember that there is a general rule. You shouldn't choose options based on what you like. Choose options based on what you think the rule is. At the start of each game, you will see two examples that will help you learn the rule. It is very important to try to stay as still as possible throughout the experiment, and to keep your eyes on the cross at the center of the screen between trials." The experimenter read the instructions aloud to participants to minimize any effects due to variability in reading proficiency. As with the ILS questions, the experimenter pointed to the instructions as he read them, in order to enhance participants' attention to the instructions (Akechi et al., 2013).

All stimuli in each block differed in terms of a single visual feature or a single semantic feature. Stimuli with the more rewarding visual feature were assigned a value of one point, as were those with the more rewarding semantic feature. Stimuli with both rewarding features were assigned a value of two points. Participants were shown examples of items with both rewarding features versus examples of items with neither rewarding feature, at the start of each block. Throughout the block, stimuli differed in reward value on the basis of one feature in each trial,

but never both. Each set of stimuli was shown to participants in a separate block. To minimize between-subjects differences, block order was fixed across participants. The blocks were arranged in sequence such that blocks that tested learning from social features of stimuli alternated with blocks that did not test learning from social features of stimuli. Blocks containing images of objects, images of faces, or words were interspersed as evenly as possible throughout the task in an attempt to limit the influence of learning during one block on learning during subsequent blocks (Table 2.1).

Block Number	Images vs. Words	Faces?	Social Learning?
1	Images	No	No
2	Images	Yes	Yes
3	Images	No	No
4	Images	No	Yes
5	Words	No	No
6	Images	Yes	Yes
7	Images	No	No
8	Images	No	Yes
9	Images	Yes	No
10	Words	No	Yes
11	Images	No	No
12	Images	Yes	Yes
13	Images	No	No
14	Images	No	Yes
15	Words	No	No
16	Images	Yes	Yes
17	Images	No	No
18	Images	No	Yes

Table 2.1. Types of stimuli presented during each block of the experimental task.

At the start of each block, participants were shown two pairs of example stimuli, with one stimulus possessing both the rewarding semantic feature and the rewarding visual feature (that is, a stimulus worth two points), and another stimulus possessing neither the rewarding semantic

feature nor the rewarding visual feature (that is a stimulus worth zero points). For instance, in one block the two visual categories were images in color and images in gray-scale, while the two semantic categories were images of food-related items and images of office-related items. Thus, for one participant, a colorful food-related item might be worth two points, a black-and-white office-related item might be worth no points, a colorful office-related item might be worth one point, and a black-and-white food-related item might be worth one point (Figure 2.1). Rewarding features were randomized across participants. Each example pair was shown to participants for 10 s in order to provide the opportunity to learn at least one of the two rules for that block. The participants were not told that the two stimuli in each pair belong to a visual and a semantic category. Each stimulus appeared in a block only once, but across a single block, the stimuli consistently belonged to one visual and one semantic category that was unique to that block.

When showing autistic participants the examples, the experimenter pointed to each stimulus on the screen, saying, “That’s worth two points. That’s worth no points,” in order to attain participants’ attention. For control participants, this was only done for blocks 1 and 10, given that control participants did not likely need additional strategies beyond the presence of the experimenter in the room to prompt them to attend to the task. The experimenter remained in the room with all participants to encourage attention to the task throughout the study session.

The task contained 18 blocks (participants had the option of a short break after 9), and after the first 2 example trials, each block contained 10 trials: 5 consisting of items that differed only with respect to the semantic category and not the visual category (e.g., two black-and-white images, one of a food-related item and one of an office-related item), and 5 consisting of items that differed only with respect to the visual category and not the semantic category (e.g., two food-related items, one in color and the other in black-and-white). The intention here was to

measure separately whether participants learned about the reward values for the visual dimensions, the semantic dimensions, both, or neither, in any particular block: the primary dependent variable was the percentage of trials in which each rewarding stimulus feature was selected in the relevant 5 trials. Participants were given no more than 3 s to choose between one of the two presented items, and the reward values were displayed above the stimuli for 2 s after a choice was made. Inter-trial intervals lasted for a random duration between 6 and 10 s, in order to provide sufficient time for pupil sizes to return to an approximate baseline in time for the subsequent trial (Figure 2.2).

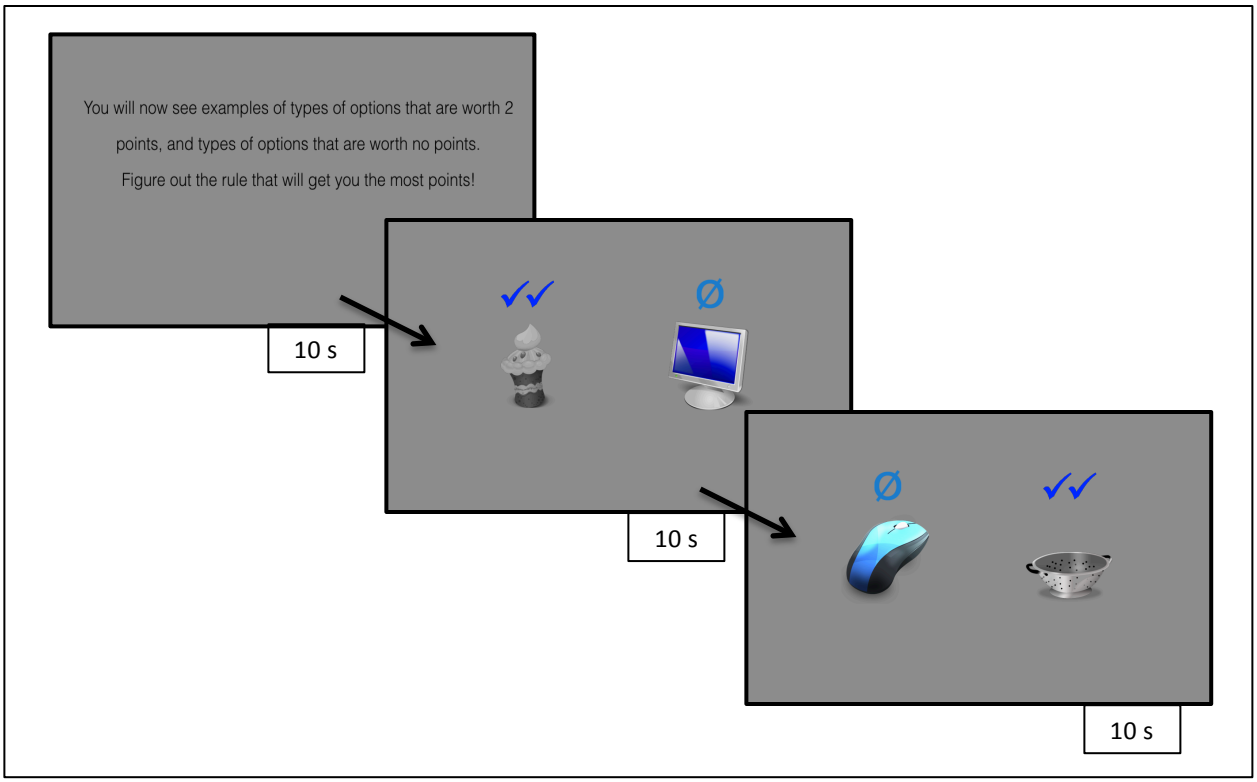


Figure 2.1. Two example trials shown at the beginning of a block. One stimulus in each pair is rewarding on both the visual and semantic dimensions, although the participants are not explicitly told this. Each frame appeared on the screen for 10 s.

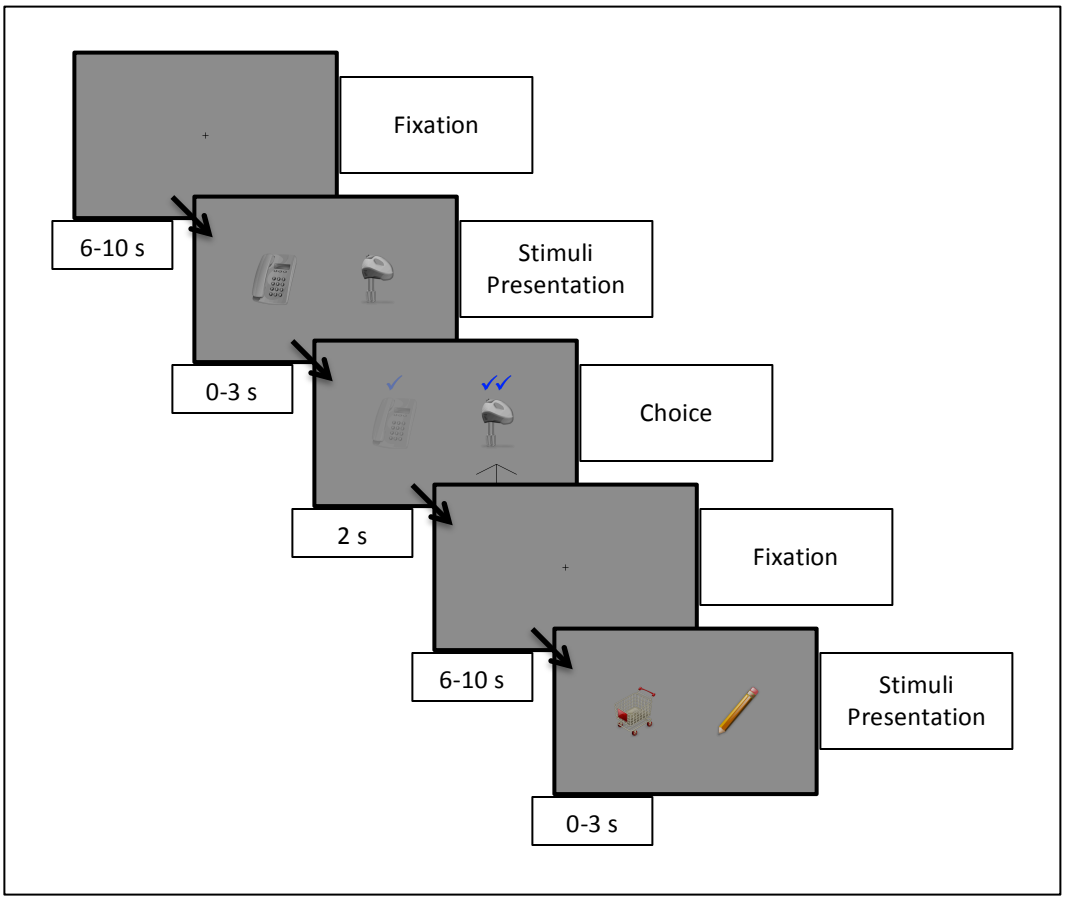


Figure 2.2. An illustration of stimuli presentation and a participant's choice.

2.4. Pupillometry Recordings

Pupillometry measurements were taken from both pupils of all participants using the Eye Tribe Tracker (The EyeTribe) and the software packages the Software Development Kit for the Eye Tribe Tracker (The EyeTribe) and the EyeTribe Toolbox for Matlab (GitHub). We used the Eye Tribe Tracker as the device is easily portable (allowing us to run the experiment at the school sites) and allows for pupillometry measurements to be taken without requiring a chinrest. Due to autistic individuals' difficulties tolerating unfamiliar sensory stimuli (Lai et al., 2014), an eye tracking system requiring a chinrest might have adversely affected autistic participants' performance. Furthermore, minimal movement of participants does not significantly impact

pupillometry recordings made by the Eye Tribe Tracker—a benefit for this investigation given that autistic individuals are likely to exhibit some repetitive movements (Lai et al., 2014). Finally, eyeglasses do not interfere with the Eye Tribe Tracker's measurements, thereby allowing us to include participants who required glasses to perform the task and easing our recruitment criteria.

To allow pupillometry measures of indigenous levels of neural gain, all stimuli in the experiment were isoluminant. All but 2 of the participants (1 of whom we excluded from the final data analysis because he did not complete the task and his performance was not better than chance) performed the task in rooms without natural sunlight. Artifacts such as eye blinks were removed from the data in a preprocessing step. Our primary dependent eye-tracking measurement was the average pupil size for both pupils. (Pupil size measurements for a single eye were used in instances in which pupil size measurements from both eyes were not recorded by the eye tracker.) To further control for variance in ambient luminance across testing sites and to differences in ambient luminance across trials due to slight head movements, baseline pupil diameter measurements were taken each time a participant began a trial and all of our analyses assessed pupil size relative to these baseline recordings.

For each participant, the eye tracker was first calibrated as indicated by the associated software. From then on, approximately 30 samples were recorded per second. Recordings were smoothed using a moving average filter with a span of 7 measurements, as done by Eldar et al. (2013a). For each trial, the baseline pupil diameter was recorded as the mean diameter of the pupil during last second of the inter-trial interval before stimulus presentation, and the pupillary response was calculated as the difference in the maximum pupil diameter measured over the course of the trial and the baseline pupil diameter. For trials in which pre-stimulus presentation

measurements from the eye tracker consisted of artifacts of longer than 400 ms (the maximum length of a human blink; Luck, 2014), all measurements from that trial were discarded.

2.5. Statistical Analyses

All statistical analyses and simulations of hypothetical probabilistic distributions were conducted in MATLAB 2014Rb (MathWorks), and all figures were generated with Microsoft Excel 365 (Microsoft), with the exception of histograms, which were generated with the Analysis ToolPak (Microsoft) in Microsoft Excel 2010 (Microsoft). Numbers of bins and bin limits were determined using the histogram function in MATLAB 2014b (MathWorks).

Unless otherwise indicated, all numerical measurements are rounded to two decimal places, and all p-values are rounded to four. Furthermore, unless otherwise noted, all inference comparisons are Student t-tests (paired for comparisons within a population and unpaired for comparisons between both populations; one-tailed for comparisons to 0.5 or 1, and two-tailed for all other comparisons, unless otherwise noted). In addition, unless otherwise stated, the correlation coefficients reported are Pearson correlation coefficients, error bars refer to the standard error of the mean (SEM), and the rejection criteria for all analyses is $p < 0.05$.

Chapter 3

Results

3.1. Task Performance: Descriptive Statistics and Inference Tests

The main learning task consisted of 18 blocks, each with 10 trials that included two unique stimuli. On every block, participants had five opportunities to choose a stimulus with the rewarding visual dimension and five opportunities to choose a stimulus with the rewarding semantic dimension. For the five trials in which there was an opportunity to learn from the visual dimension of stimuli, we recorded the proportion of such trials in which participants chose the stimulus with the rewarding visual feature, and for the five trials in which there was an opportunity to learn from the semantic dimension of stimuli, we recorded the proportion of such trials in which participants chose the stimuli with the rewarding semantic feature (Tables 3.1 and 3.2; Figure 3.1). At this step, we excluded from all further analyses the data from 2 autistic participants who not only failed to complete all blocks of the task, but also performed at levels that were not above chance for either dimension (Appendix C). Any reference to "all participants" in subsequent analyses assumes the exclusion of these individuals.

In order to ascertain that all autistic participants, all control participants, and the collective sample of both autistic and control participants successfully performed on both the visual and semantic dimensions of stimuli in all blocks, the mean performance levels were computed on each dimension across these three groups, for each block (Table 3.3; Figures 3.2 and 3.3). One-tailed t-tests were conducted to determine if the mean performance on each dimension for each block was significantly above 0.5 (chance performance). Across all blocks, the mean performance of each participant was significantly higher than 0.5 for at least one

dimension, indicating that as a whole, all participants individually learned from at least one dimension on each block. Therefore, we did not initially discard any blocks in the below analyses (Table 3.3).

Autistic Participant	Visual Performance (mean ± SEM)	Semantic Performance (mean ± SEM)
1	(57.78 ± 4.24)%*	(58.89 ± 4.71)%*
2	(63.33 ± 6.10)%*	(58.89 ± 5.48)%
3	(58.89 ± 6.36)%	(55.56 ± 5.73)%
4	(44.44 ± 5.73)%	(58.89 ± 4.71)%*
5	(61.11 ± 5.48)%*	(50.00 ± 4.35)%
6	(58.89 ± 5.23)%	(55.56 ± 5.50)%
7	(54.44 ± 6.01)%	(60.00 ± 7.05)%
8	(53.33 ± 7.05)%	(61.11 ± 6.36)%*
9	(55.56 ± 5.25)%	(61.11 ± 4.71)%*
10	(64.44 ± 5.95)%*	(70.00 ± 6.31)%*
Mean Performance	**(57.22 ± 1.82)%****	**(59.00 ± 1.62)%*****

Table 3.1. Autistic participants' individual performances for learning on each dimension. For one-tailed t-test comparisons of performance to 0.5, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Control Participant	Visual Performance (mean ± SEM)	Semantic Performance (mean ± SEM)
1	(56.67 ± 6.72)%	(78.89 ± 4.11)%*
2	(68.89 ± 7.62)%*	(77.78 ± 6.45)%*
3	(75.56 ± 6.77)%*	(77.78 ± 6.03)%*
4	(58.89 ± 4.71)%*	(81.11 ± 5.71)%*
5	(68.89 ± 6.71)%*	(64.44 ± 6.77)%*
6	(76.67 ± 6.10)%*	(76.67 ± 5.89)%*
7	(65.56 ± 5.06)%*	(78.89 ± 6.95)%*
8	(78.89 ± 5.23)%*	(86.67 ± 3.96)%*
9	(66.67 ± 7.41)%*	(77.78 ± 6.24)%*
10	(85.56 ± 4.52)%*	(75.56 ± 5.73)%*
Mean Performance	**(70.22 ± 2.85)%*****	**(77.56 ± 1.75)%*****

Table 3.2. Control participants' individual performances for learning on each dimension. For one-tailed t-test comparisons of performance to 0.5, * $p < 0.05$, *** signifies $p < 0.001$.

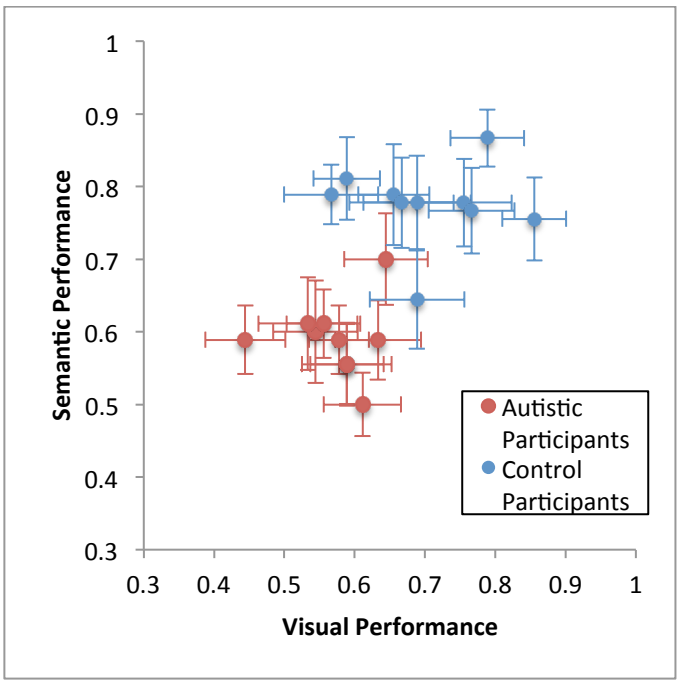


Figure 3.1. Mean learning performances for each participant, across all blocks.

Block	Dimension	Autistic Participants' Performance (mean ± SEM); (t-test vs. 0.5)	Control Participants' Performance (mean ± SEM); (t-test vs. 0.5)	All Participants' Performance (mean ± SEM); (t-test vs. 0.5)
1	Visual	(44.00 ± 4.99)% p = 0.8701	(54.00 ± 6.70)% p = 0.2826	(49.00 ± 4.22)% p = 0.5923
	Semantic	(56.00 ± 8.33)% p = 0.2447	(76.00 ± 6.53)% p = 0.0016	(66.00 ± 5.64)% p = 0.0053
2	Visual	(48.00 ± 6.11)% p = 0.6245	(48.00 ± 8.54)% p = 0.5900	(48.00 ± 5.11)% p = 0.6501
	Semantic	(72.00 ± 4.22)% p = 0.0003	(84.00 ± 4.00)% p ≈ 0	(78.00 ± 3.21)% p ≈ 0
3	Visual	(70.00 ± 6.83)% p = 0.0084	(74.00 ± 5.21)% p = 0.0001	(72.00 ± 4.21)% p ≈ 0
	Semantic	(46.00 ± 6.70)% p = 0.7174	(64.00 ± 7.18)% p = 0.0415	(55.00 ± 5.21)% p = 0.1745
4	Visual	(62.00 ± 7.57)% p = 0.0737	(82.00 ± 6.29)% p = 0.0003	(72.00 ± 5.31)% p = 0.0003
	Semantic	(42.00 ± 6.29)% p = 0.8824	(88.00 ± 6.11)% p = 0.0001	(65.00 ± 6.79)% p = 0.0198
5	Visual	(50.00 ± 6.15)%	(72.00 ± 6.80)%	(61.00 ± 5.12)%

Block	Dimension	Autistic Participants' Performance (mean ± SEM); (t-test vs. 0.5)	Control Participants' Performance (mean ± SEM); (t-test vs. 0.5)	All Participants' Performance (mean ± SEM); (t-test vs. 0.5)
5	Visual	p = 0.5000	p = 0.0051	p = 0.0225
	Semantic	(44.00 ± 9.33)% p = 0.7318	(60.00 ± 6.67)% p = 0.0839	(52.00 ± 5.88)% p = 0.3687
6	Visual	(46.00 ± 6.70)% p = 0.7174	(62.00 ± 8.14)% p = 0.0872	(54.00 ± 5.45)% p = 0.2359
	Semantic	(62.00 ± 8.67)% p = 0.0998	(88.00 ± 6.80)% p = 0.0002	(75.00 ± 6.13)% p = 0.0003
7	Visual	(68.00 ± 7.42)% p = 0.0192	(84.00 ± 9.33)% p = 0.0027	(76.00 ± 6.09)% p = 0.0002
	Semantic	(68.00 ± 8.54)% p = 0.0321	(88.00 ± 6.11)% p = 0.0001	(78.00 ± 5.60)% p ≈ 0
8	Visual	(52.00 ± 6.11)% p = 0.3755	(82.00 ± 6.96)% p = 0.0006	(67.00 ± 5.67)% p = 0.0037
	Semantic	(46.00 ± 11.18)% p = 0.6357	(68.00 ± 8.00)% p = 0.0255	(57.00 ± 7.15)% p = 0.1699
9	Visual	(62.00 ± 5.54)% p = 0.0292	(54.00 ± 6.70)% p = 0.2826	(58.00 ± 4.33)% p = 0.0401
	Semantic	(58.00 ± 8.67)% p = 0.1900	(96.00 ± 2.67)% p ≈ 0	(77.00 ± 6.20)% p = 0.0002
10	Visual	(48.00 ± 8.00)% p = 0.5959	(54.00 ± 9.45)% p = 0.3410	(51.00 ± 6.07)% p = 0.4354
	Semantic	(68.00 ± 6.80)% p = 0.0133	(94.00 ± 3.06)% p ≈ 0	(81.00 ± 4.70)% p ≈ 0
11	Visual	(62.00 ± 11.33)% p = 0.1586	(72.00 ± 6.80)% p = 0.0051	(67.00 ± 6.53)% p = 0.0088
	Semantic	(62.00 ± 6.29)% p = 0.0444	(74.00 ± 8.46)% p = 0.0097	(68.00 ± 5.31)% p = 0.0015
12	Visual	(52.00 ± 8.54)% p = 0.4100	(94.00 ± 3.06)% p ≈ 0	(73.00 ± 6.53)% p = 0.0011
	Semantic	(68.00 ± 7.42)% p = 0.0192	(98.00 ± 2.00)% p ≈ 0	(83.00 ± 5.08)% p ≈ 0
13	Visual	(48.00 ± 8.00)% p = 0.5959	(54.00 ± 10.77)% p = 0.3595	(51.00 ± 6.57)% p = 0.4403
	Semantic	(58.00 ± 4.67)%	(70.00 ± 9.07)%	(64.00 ± 5.15)%

Block	Dimension	Autistic Participants' Performance (mean ± SEM); (t-test vs. 0.5)	Control Participants' Performance (mean ± SEM); (t-test vs. 0.5)	All Participants' Performance (mean ± SEM); (t-test vs. 0.5)
13	Semantic	p = 0.0603	p = 0.0274	p = 0.0068
14	Visual	(64.00 ± 7.77)% p = 0.0526	(96.00 ± 2.67)% p ≈ 0	(80.00 ± 5.43)% p ≈ 0
	Semantic	(66.00 ± 4.27)% p = 0.0023	(46.00 ± 8.46)% p = 0.6762	(56.00 ± 5.15)% p = 0.1292
15	Visual	(50.00 ± 10.43)% p = 0.5000	(58.00 ± 7.57)% p = 0.1591	(54.00 ± 6.34)% p = 0.2678
	Semantic	(66.00 ± 6.70)% p = 0.0203	(92.00 ± 4.42)% p ≈ 0	(79.00 ± 4.92)% p ≈ 0
16	Visual	(58.00 ± 7.57)% p = 0.1591	(86.00 ± 4.27)% p ≈ 0	(72.00 ± 5.31)% p = 0.0003
	Semantic	(62.00 ± 3.59)% p = 0.0043	(90.00 ± 3.33)% p ≈ 0	(76.00 ± 4.00)% p ≈ 0
17	Visual	(66.00 ± 6.00)% p = 0.0129	(54.00 ± 9.45)% p = 0.3410	(60.00 ± 5.62)% p = 0.0456
	Semantic	(56.00 ± 7.77)% p = 0.2300	(50.00 ± 8.56)% p = 0.5000	(53.00 ± 5.67)% p = 0.3015
18	Visual	(80.00 ± 6.67)% p = 0.0007	(84.00 ± 8.33)% p = 0.0014	(82.00 ± 5.21)% p ≈ 0
	Semantic	(62.00 ± 5.54)% p = 0.0292	(70.00 ± 8.03)% p = 0.0172	(66.00 ± 4.83)% p = 0.0018

Table 3.3. Mean performance across participants on each dimension, for each block of the task. P-values indicate comparisons of the mean performance in question to 0.5.

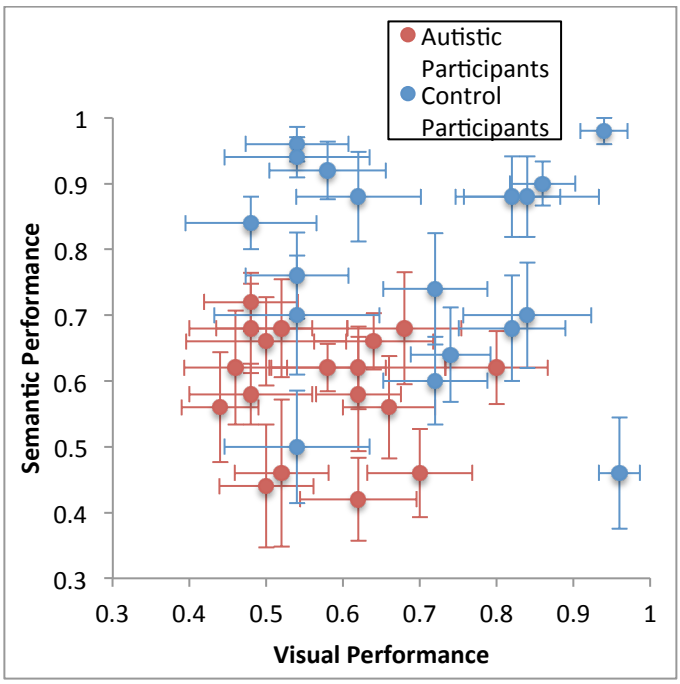


Figure 3.2. Mean learning performances for each block, across each respective sample of participants.

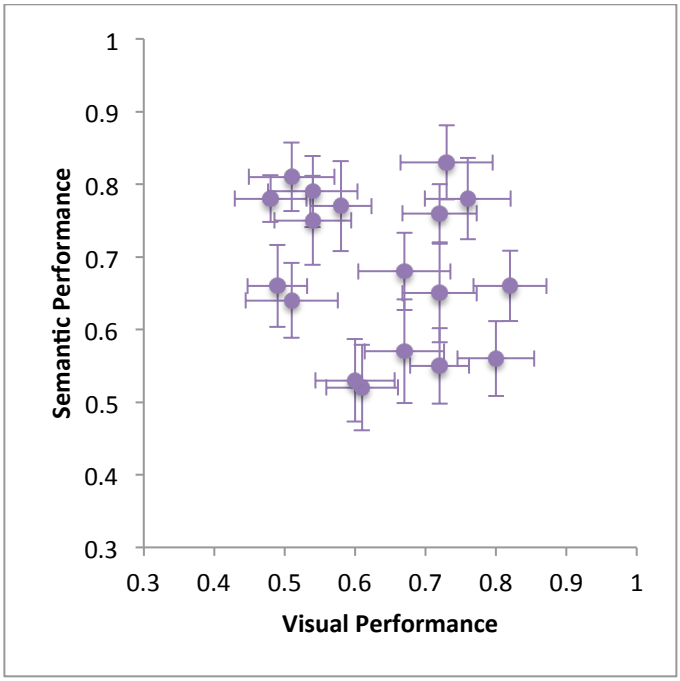


Figure 3.3. Mean learning performances for each block, across all participants.

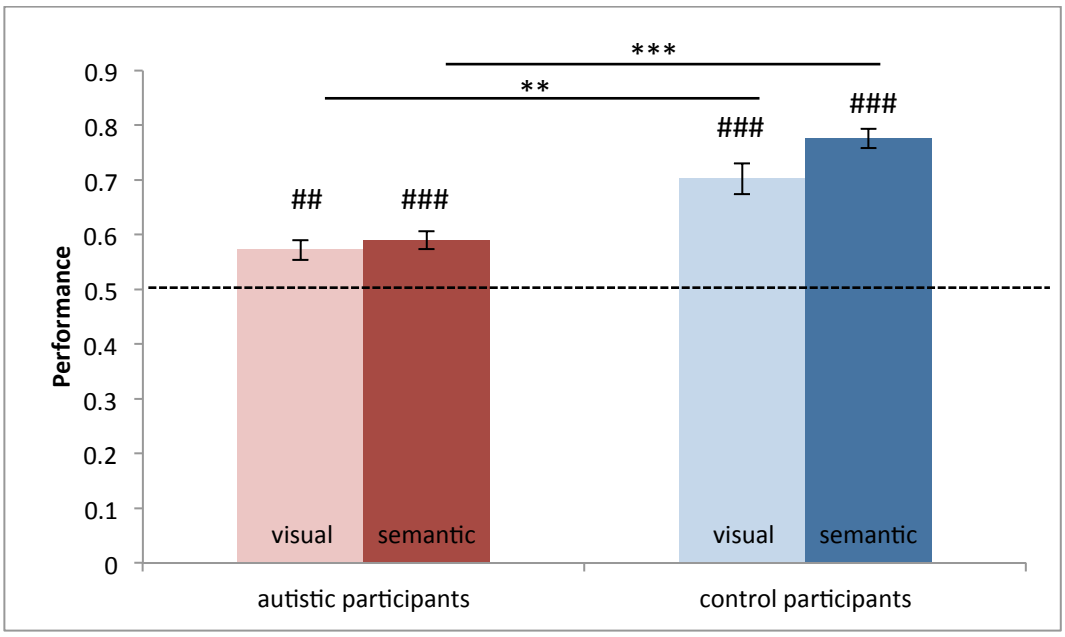


Figure 3.4. Mean learning performances for all blocks, across all participants. *'s are used for comparisons between dimensions/groups, and #'s are used for comparisons to 0.5. ** and ## signify $p < 0.01$, and *** and ### signify $p < 0.001$.

We then performed the same analyses described above separately for those blocks in which the semantic features of stimuli were social in nature and those in which semantic features were non-social in nature (Table 2.1; Appendix B), to see if social stimuli impacted learning on either dimension. Mean visual performance of all autistic participants was significantly higher than 0.5 for both social (mean ± SEM = 56.67% ± 1.91%; $p = 0.0034$) and nonsocial (mean ± SEM = 57.78% ± 2.73%; $p = 0.0096$) blocks, and mean semantic performance of all autistic participants was also significantly higher than 0.5 for both social (mean ± SEM = 60.89% ± 2.59%; $p = 0.0012$) and nonsocial (mean ± SEM = 57.11% ± 2.25%; $p = 0.0057$) blocks. Likewise, mean visual performance of all control participants was significantly higher than 0.5 for both social (mean ± SEM = 76.44% ± 3.00%; $p \approx 0$) and nonsocial (mean ± SEM = 64.00% ± 3.23%; $p = 0.0009$) blocks, and mean semantic performance of all control participants was also significantly higher than 0.5 for both social (mean ± SEM = 80.67% ± 1.66%; $p \approx 0$) and

nonsocial (mean ± SEM = 74.44% ± 2.51%; $p \approx 0$) blocks. In other words, all participants effectively learned from either dimension, regardless of whether the difference in semantic feature was social or nonsocial in nature.

For each group, we then conducted a two-way analysis of variance (ANOVA) to compare both visual and semantic learning performances on both social and nonsocial blocks. Among autistic participants, there were no significant differences in either visual or semantic performance across social and nonsocial blocks ($F = 0.55$; $p = 0.4621$), nor were there significant differences in performance on either social or nonsocial blocks across instances of visual and semantic learning ($F = 0.31$; $p = 0.5806$). In contrast, among control participants, semantic performance was significantly higher than visual performance across social and nonsocial blocks ($F = 7.56$; $p = 0.0093$), and performance was significantly superior during social—as opposed to nonsocial—blocks across instances of visual and semantic learning ($F = 12.25$; $p = 0.0013$). There were no interaction effects between stimulus dimension and block type for either autistic participants ($F = 1.04$; $p = 0.3136$) or control participants ($F = 1.36$; $p = 0.2511$). Therefore, these findings indicate that overall, while control participants learned more readily from social stimuli, the sociality of the semantic feature of stimuli did not have an effect on autistic participants' learning capabilities in our task.

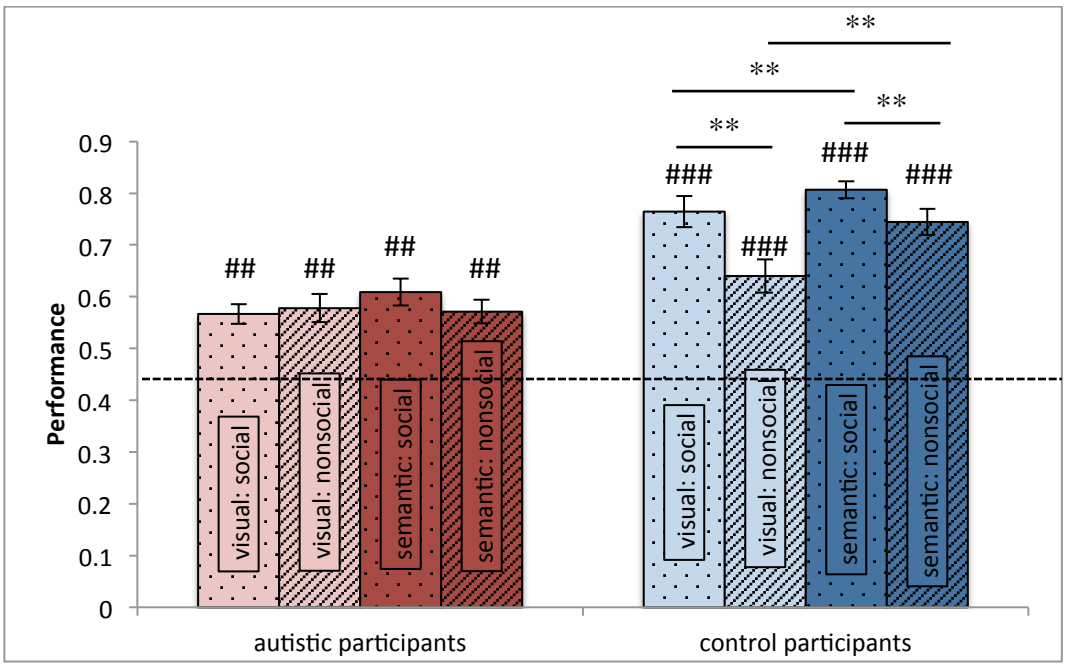


Figure 3.5. Mean learning performances of social, and nonsocial blocks, each across all participants. *'s are used for comparisons between dimensions/block types, and #'s are used for comparisons to 0.5. ** and ## signify $p < 0.01$, and ### signifies $p < 0.001$.

3.2. Task Performance: Learning Simulations

Given our hypothesis that autistic individuals are more often (or constitutively) in a state of high gain in which their learning should be focused on predisposed dimensions, we would expect autistic participants to most frequently learn from either the visual features or semantic features of stimuli (depending on personal predispositions, but rarely both; Eldar et al., 2013a), while we would anticipate that some control participants are equally likely to learn from one feature of the stimuli or both (a behavior associated with the low neural gain state; Eldar et al., 2013a).

The performance data neither support nor disprove this hypothesis. Assuming that individual participants vary in their predisposition to attend to the visual or semantic features of the multidimensional stimuli in our task, we would not anticipate a priori that there be a significant difference between visual and semantic performance in either group. That is, all else

equal, we would expect that approximately 50% of autistic participants (assuming they are all in the high gain state) would attend primarily to the visual features of stimuli, while the remaining 50% would attend mostly to the semantic features of stimuli. On the other hand, control participants that are either in high or low gain states (Eldar et al., 2013a) would equally likely be attending to either or both stimulus dimensions at a given time, again suggesting approximately equal levels of learning about semantic and visual features across the population. Autistic participants' significantly lower performance than control participants' performance might be a reflection of autistic individuals' general poorer understanding of the task instructions. Alternatively, the between-groups effect might be a consequence of the fact that fewer participants were able to learn about both dimensions in the autistic group, as compared to the control group. We thereby ran two simulations. Our first simulation assumed that autistic participants only learn from one stimulus feature or the other, whereas control participants can learn from one feature, the other, or both. Our second simulation, on the other hand, assumed that both autistic and control participants are equally likely to be learning from one stimulus feature, the other, or both. We assessed whether a between-groups performance effect could be observed in either data simulation.

To calculate each simulated participant's performance, 50 random numbers between 0 and 1 were generated on each dimension, 18 times (each 50-sample distribution of random numbers representing each of the 18 blocks in our task). When assuming that a participant successfully learned from a dimension, we computed the proportion of values in each 50-number sample that were less than the actual group mean performance on that dimension. On the other hand, when assuming that a participant did not successfully learn from a dimension, we computed the proportion of values in each sample that were less than 0.5 (performance at

chance). Thus, we could simulate participant performances for cases in which individuals are learning on one dimension, the other dimension, or both.

The first simulation was run for 10 autistic participants and 9 control participants. (We chose a sample size of 9 for the control group, so that an equal number of control participants could be simulated to learn from one stimulus feature, the other, or both.) For each set of 18 simulated blocks, we assumed that 5 autistic participants would perform at chance on the visual dimension while approximately performing equivalent to the actual group mean semantic performance, whereas the remaining 5 autistic participants would perform at chance on the semantic dimension while approximately performing equivalent to the actual group mean visual performance. Furthermore, we assumed that 3 control participants would perform at chance on the visual dimension while approximately performing equivalent to the actual group mean semantic performance, 3 control participants would perform at chance on the semantic dimension while approximately performing equivalent to the actual group mean visual performance, and 3 control participants would perform at success rates approximately equivalent to the actual group mean performances on both dimensions. The simulation was run 10,000 times. We computed the mean and SEM performance on each dimension, for each simulation. Likewise, we conducted one-tailed t-tests comparing performances to 0.5 and two-tailed t-tests comparing visual and semantic performances within a group, and comparing performances between groups. Descriptive statistics and p-values for each simulation were averaged together, denoted as “average mean,” “average SEM,” and “average p-value” below.

The average of the mean performances for the autistic group across all simulations was significantly higher than 0.5 on both visual (average mean ± average SEM = 53.61% ± 0.69%; average $p \approx 0$) and semantic (average mean ± average SEM = 54.50% ± 0.69%; average $p \approx 0$)

dimensions. Likewise, the control group's average of mean performances across all simulations was significantly higher than 0.5 on both visual (average mean ± average SEM = 62.14% ± 0.66%; average $p \approx 0$) and semantic (average mean ± average SEM = 67.44% ± 0.62%; average $p \approx 0$) dimensions. Performance on the semantic dimension was significantly higher than that on the visual dimension for the simulated control participants (average $p = 0.0002$), but not for the simulated autistic participants (average $p = 0.3232$; Figure 3.6). In addition, the simulated control group exhibited significantly higher performance than the simulated autistic group on both visual (average $p \approx 0$) and semantic (average $p \approx 0$) dimensions.

We then ran a comparative simulation that assumed 9 autistic and 9 control participants were all equally likely to exhibit learning behaviors characteristic of either the high or low gain states. For each set of 18 simulated blocks, we assumed that 3 autistic and 3 control participants would perform at chance on the visual dimension, while approximately performing equivalent to their actual respective mean semantic performances. In addition, we assumed 3 autistic and 3 control participants would perform at chance on the semantic dimension, while approximately performing at success rates equivalent to their actual respective mean visual performances. Finally, we assumed that the remaining participants would perform approximately equivalent to their actual respective mean performances on both dimensions. This simulation was designed and executed according to the procedure described above. This simulation was also ran 10,000 times. Again, means, SEMs, and p-values were computed separately for each simulation, before being averaged together.

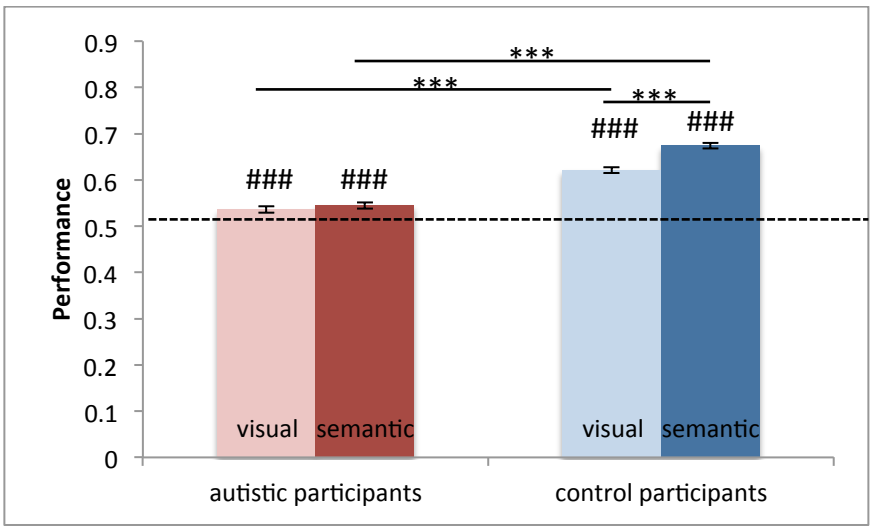


Figure 3.6. Simulation assuming that autistic participants are learning from only one stimulus dimension and control participants are learning from either one or two dimensions. *'s are used for comparisons between dimensions/groups, and #'s are used for comparisons to 0.5. *** and ### signify $p < 0.001$.

The average of the mean performances for autistic participants across all simulations was again significantly higher than 0.5 on both visual (average mean ± average SEM = 54.82% ± 0.73%; average $p \approx 0$) and semantic (average mean ± average SEM = 56.00% ± 0.73%; average $p \approx 0$) dimensions. Likewise, control participants' average of mean performances across all simulations was again significantly higher than 0.5 on both visual (average mean ± average SEM = 63.48% ± 0.73%; average $p \approx 0$) and semantic (average mean ± average SEM = 68.37% ± 0.69%; average $p \approx 0$) dimensions. Simulated control participants again exhibited significantly higher performances than simulated autistic participants on both visual (average $p \approx 0$) and semantic (average $p \approx 0$) dimensions. Performance on the semantic dimension was again significantly higher than that on the visual dimension across the simulated control participants (average $p \approx 0$), but not across the simulated autistic participants (average $p = 0.2498$; Figure 3.7).

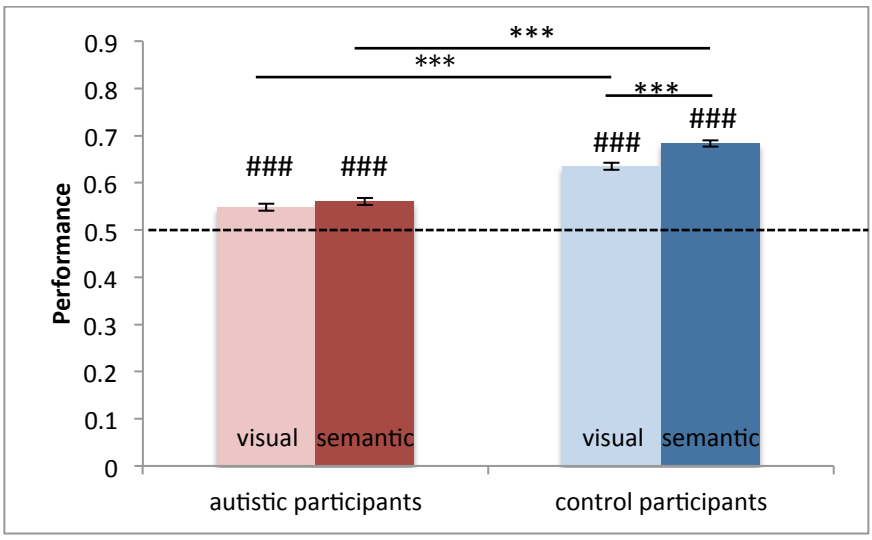


Figure 3.7. Simulation assuming that autistic participants and control participants are both equally likely to learn from either one or two dimensions of stimuli. *'s are used for comparisons between dimensions/groups, and #'s are used for comparisons to 0.5. *** and ### signify $p < 0.001$.

Given that both simulations were representative of our original data, we were thereby not able to use the simulations to infer whether autistic participants attended to either one or both features of the multidimensional stimuli in our task, when learning.

3.3. Task Performance: Covariance Between Performance on Semantic and Visual Dimensions

If autistic participants are constitutively in a state of high neural gain, we might expect their visual performance on our task to be inversely correlated to their semantic performance, given that these individuals can only attend to one stimulus dimension at a time. In contrast, control participants' visual and semantic performances should be more independent of each other, at least to the extent that some of these participants are predominantly in a state of low gain. To test this, we tested several measures of the correlation between learning performance on the two dimensions for each participant, and assessed the statistical significance of these measures at the group level against a null distribution generated by permutations of the data.

We assessed the covariance between learning on the two dimensions using three different measures that might potentially differ between autistic participants and control participants if individuals with autism constitutively exhibit behaviors consistent of high gain: 1) the absolute difference between mean semantic performance and mean visual performance (what we will henceforth refer to as "dimensional learning difference"), 2) the covariance between mean semantic performance and mean visual performance, and 3) the correlation coefficient between mean semantic performance and mean visual performance. For autistic participants, the dimensional learning difference was 26.44%, the covariance was -0.000261, and the correlation coefficient was -0.0346, whereas these measures among control participants were 30.89%, -0.0070, and -0.1037, respectively.

To compute the null distribution for these three measures, we randomly permutated the visual performance on the 18 blocks within each participant, and recalculated the three measures. We repeated this procedure 10,000 times for each participant. That is, we generated 10,000 performance measures, each containing the same performance values, but randomized so that each visual performance value on a select block might be paired with a semantic performance value from any of the other 18 blocks. For each randomization of blocks, we computed the absolute difference, covariance, and correlation coefficient with respect to the mean semantic performance and mean visual performance, for both autistic participants and control participants.

Across the respective randomized distributions of block permutations for autistic participants, the mean absolute difference was again 26.44%, the covariance was -0.00007, and the correlation coefficient was -0.0012, whereas such measures across control participants were 28.92%, 0.000107, and 0.0019, respectively. The true dimensional learning differences, covariance values, and correlation coefficients of performance were within the 95% confidence

interval of each respective aforementioned distribution for both the autistic ($p = 0.4691$, $p = 0.4841$, and $p = 0.3302$, respectively; Figures 3.8, 3.9, and 3.10) and control ($p = 0.8290$, $p = 0.1626$, and $p = 0.1575$, respectively; Figures 3.11, 3.12, and 3.13) groups. We also compared the differences between the actual mean dimensional learning difference, covariance, and correlation coefficient of performance across autistic participants versus across control participants, to the differences between the mean of the randomized distributions of the absolute dimensional learning difference, covariance, and correlation coefficient across autistic participants versus across control participants. These comparisons yielded no differences between the autistic and control groups ($p = 0.9997$, $p = 0.2090$, and $p = 0.2952$, respectively). We therefore did not find support in our data for a stronger covariance between visual and semantic learning in autistic individuals as compared to neurotypical control participants.

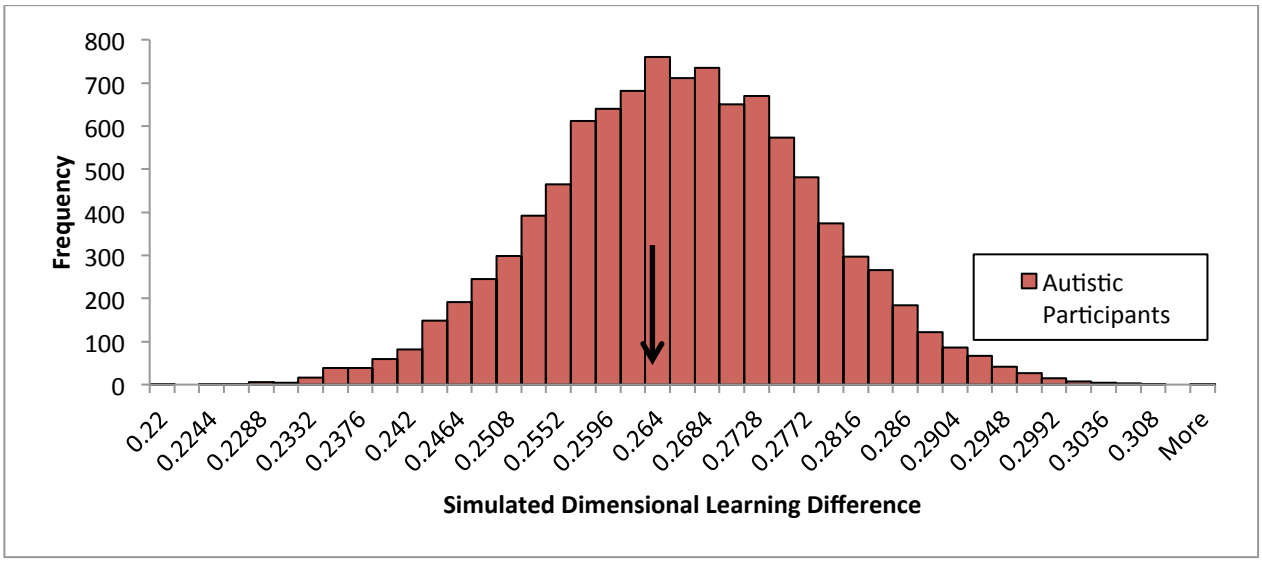


Figure 3.8. Distribution of the absolute difference between mean semantic performance and mean visual performance of autistic participants for 10,000 independent randomizations of block orderings. The arrow indicates the actual difference.

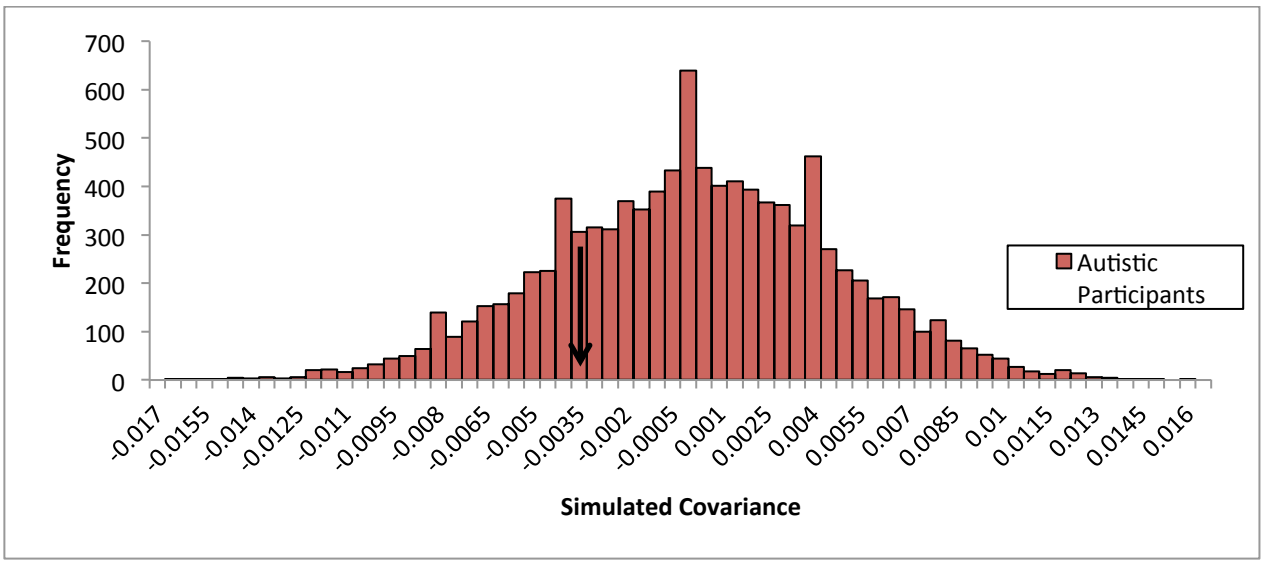


Figure 3.9. Distribution of the covariance values between mean semantic performance and mean visual performance of autistic participants for 10,000 independent randomizations of block orderings. The arrow indicates the actual covariance.

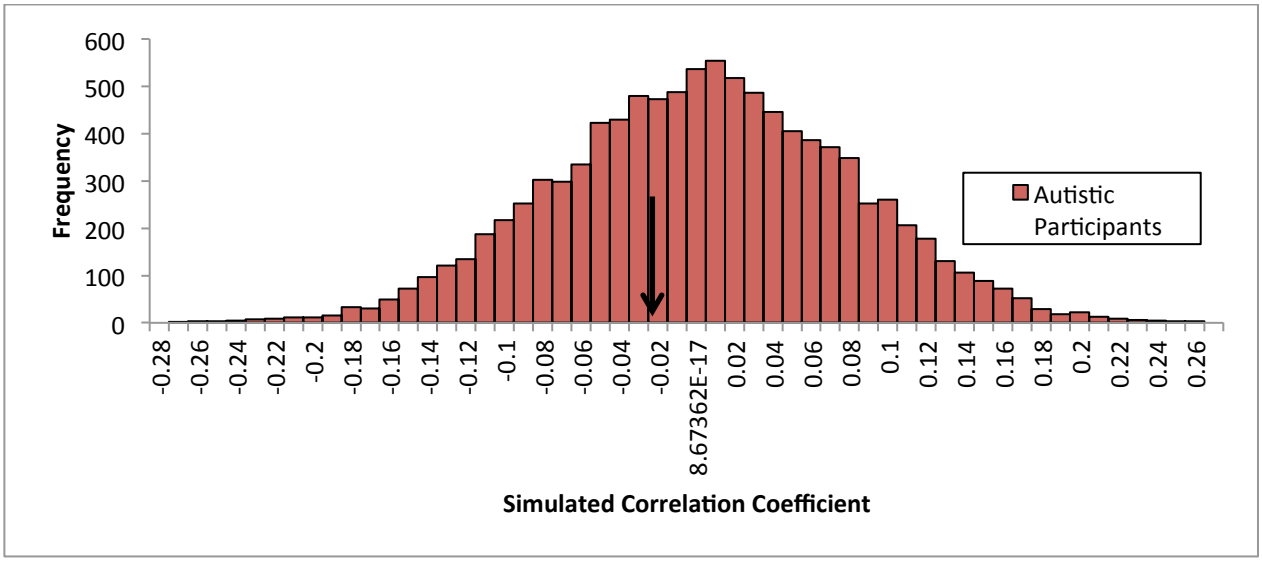


Figure 3.10. Distribution of the correlation coefficient between mean semantic performance and mean visual performance of autistic participants for 10,000 independent randomizations of block orderings. The arrow indicates the actual correlation coefficient.

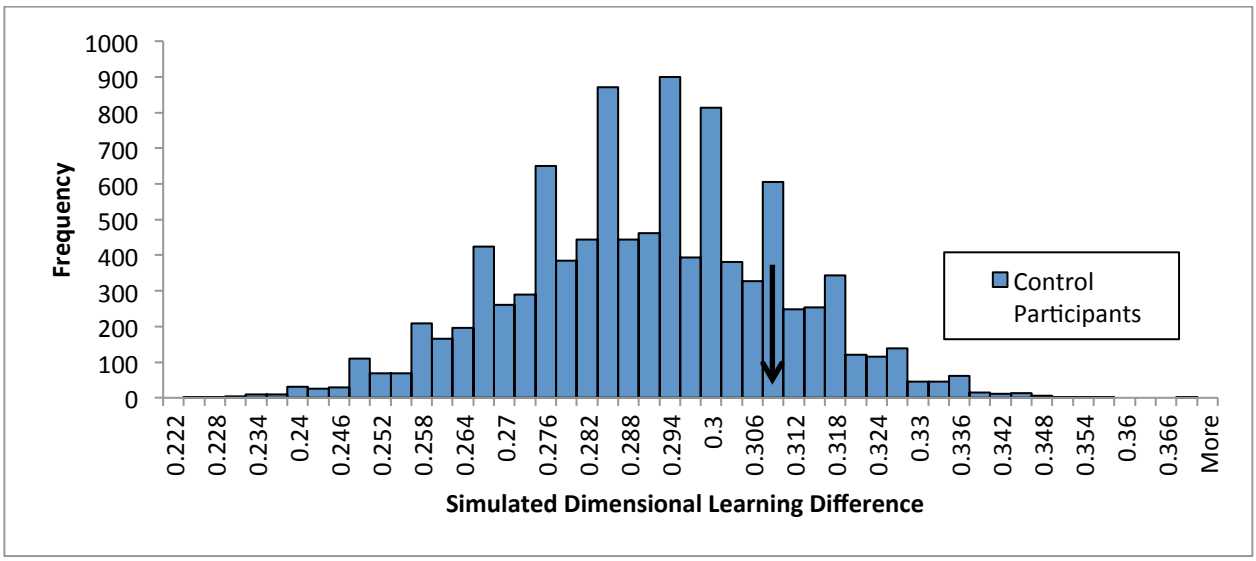


Figure 3.11. Distribution of the absolute difference between mean semantic performance and mean visual performance of control participants for 10,000 independent randomizations of block orderings. The arrow indicates the actual absolute difference.

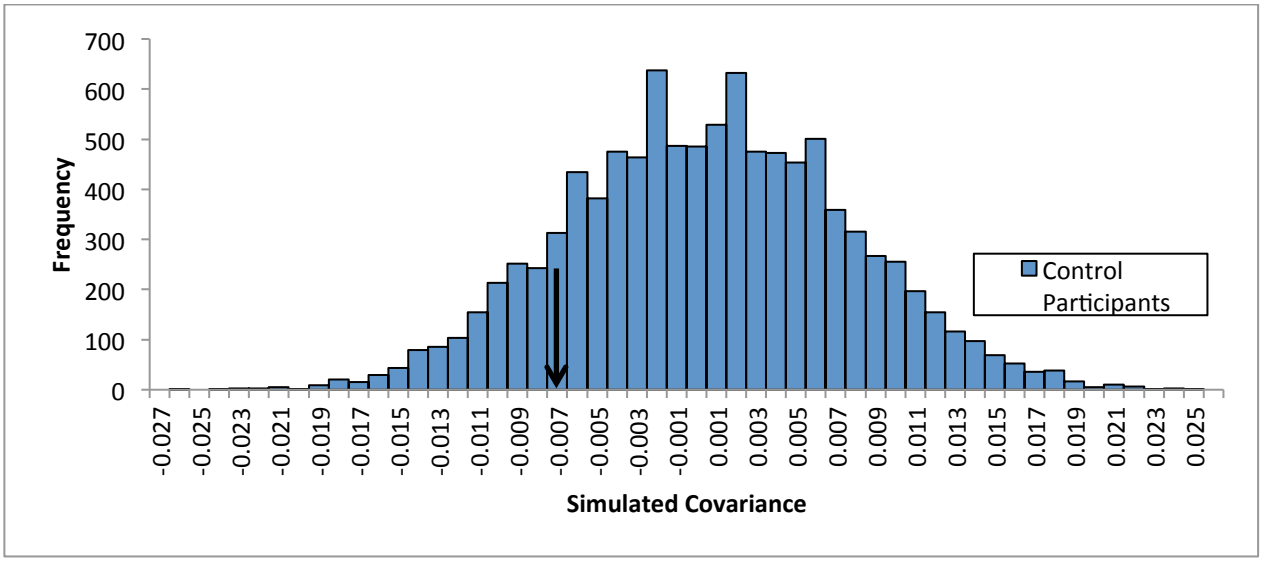


Figure 3.12. Distribution of the covariance values between mean semantic performance and mean visual performance of control participants for 10,000 independent randomizations of block orderings. The arrow indicates the actual covariance.

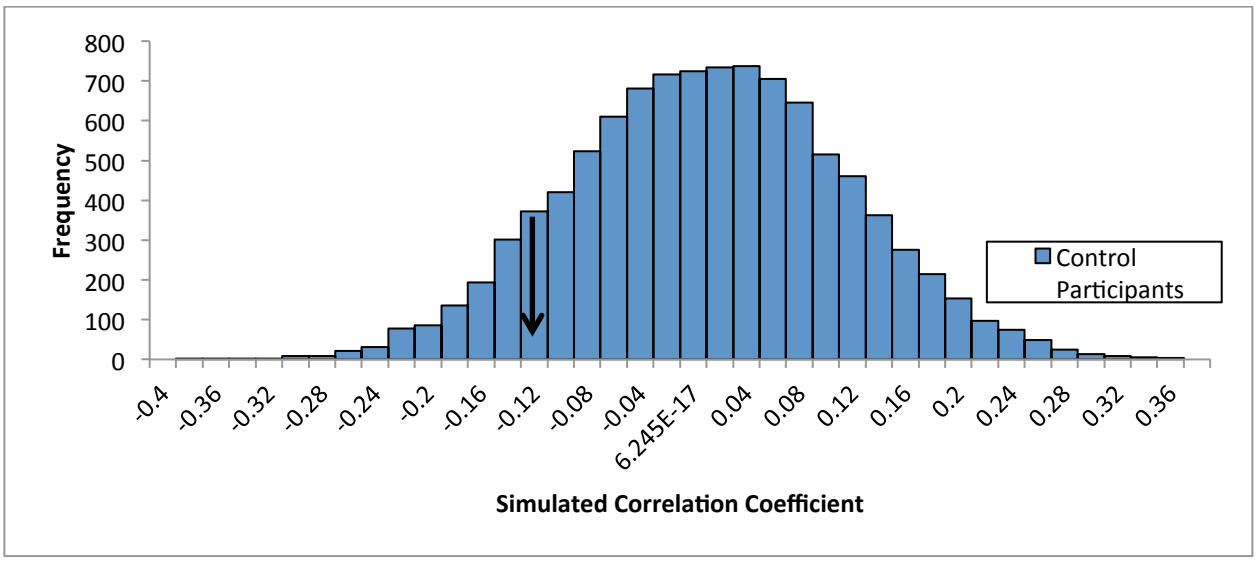


Figure 3.13. Distribution of the correlation coefficient between mean semantic performance and mean visual performance of control participants for 10,000 independent randomizations of block orderings. The arrow indicates the actual correlation coefficient.

Given that none of the aforementioned comparisons were statistically significant, we could not use these permutation analyses to determine whether in fact visual performance and semantic performance co-vary with one another across either the autistic or control groups.

3.4. Task Performance: Analyses Matched on Performance

While evidence that autistic individuals learn with a more narrow breadth of attention would support the idea that such individuals are constitutively in the high neural gain state, we might not be able to observe this behavioral effect given the main effects of overall performance across the two groups of participants in our experimental task (Figure 3.4). Therefore, we repeated our main analyses on a subset of the blocks for which overall performance of the two groups was matched. To do this, for autistic participants we discarded data from blocks in which autistic participants performed significantly lower than control participants, and for control participants we discarded blocks in which they performed significantly higher than autistic participants. Our justification for this procedure is that while participants in each group were

relatively matched on age (Section 2.1), participants were not necessarily matched on learning ability. Given that autistic participants had significantly poorer performance on our task than control participants, the aforementioned sub-selection of blocks is analogous to testing autistic participants only on the easier blocks while testing the control participants only on on the more difficult blocks. The goal was to select a subset of data such that, in general, the two groups would encounter the same level of subjective difficulty when performing our task, thereby allowing us to assess how each group approached learning the task, comparatively.

For these analyses, different sets of blocks were chosen for each population. Blocks chosen for autistic participants were those for which the mean performance ± SEM that intersected with both the mean ± SEM of autistic participants' performance on another block, and the mean ± SEM of control participants' performance on the same block or another block. We also required that the two blocks with such confidence intervals that intersect with the original candidate block must also have 95% confidence intervals that intersect with the mean ± SEM of autistic participants' performance on a block that meets the aforementioned criteria, and the mean ± SEM of control participants' performance on a block that meets the aforementioned criteria. That is, all eligible blocks for these analyses have 95% performance confidence intervals that overlap with 95% performance confidence intervals of at least one block from both participant groups, each of which overlaps with 95% performance confidence intervals of at least one block from both participant groups, and so forth. 11 autistic and 7 control participants' performance blocks met these criteria. In order to maintain the same number of blocks for each participant group in our analyses, we computed the average of the mean visual performance and mean semantic performance for each of the 11 autistic participants' performance blocks, and then discarded the 4 blocks with the lowest values for this average. (The lowest values were

54.00%, 58.00%, and 60.00%. Given that multiple autistic participants' performance blocks had an average of the mean visual performance and mean semantic performance equal to 60.00%, of these blocks, we discarded the one in which participants performed at less than chance on one of the dimensions.) Therefore, for the below analyses, the final selection of autistic participants' performance blocks included blocks 7, 11, 12, 14, 16, 17, and 18, and the final selection of control participants' performance blocks included blocks 1, 3, 5, 8, 11, 13, and 18 (Figure 3.14; Appendix B).

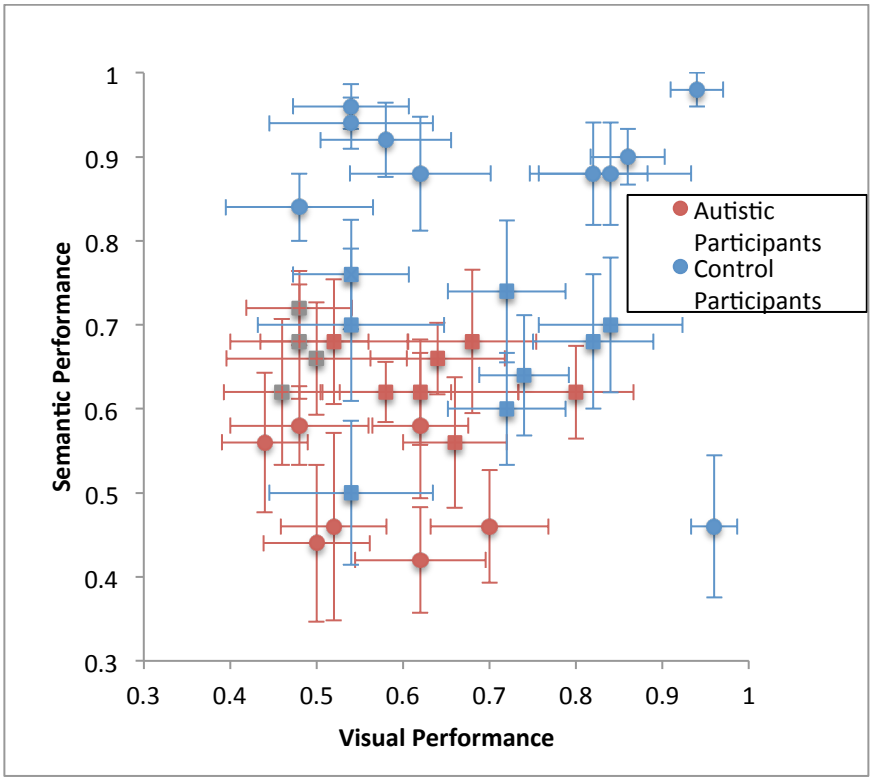


Figure 3.14. Mean learning performance across blocks, for each population of participants. Blocks selected for the matched performance analyses are indicated by squares. Blocks that were not selected are indicated by circles. Squares with gray shading indicate blocks that met the criteria for the matched performance analyses but were excluded in order to maintain the same number of blocks for each group.

Across autistic participants, performance was significantly higher than 0.5 on both visual (mean ± SEM = 64.29% ± 2.87%; p = 0.0004) and semantic (mean ± SEM = 63.43% ± 2.29%; p = 0.0001) dimensions. Likewise, across control participants, performance was also significantly higher than 0.5 on both visual (mean ± SEM = 70.29% ± 4.75%; p = 0.0010) and semantic (mean ± SEM = 68.86% ± 3.42%; p = 0.0002) dimensions. In other words, learning occurred across the selected blocks, on both dimensions, across all participants. A within-groups comparison of performances on the two dimensions showed no significant differences in visual and semantic performance both across autistic participants (p = 0.8056) and control participants (p = 0.8362). We did not test differences in performances during social and nonsocial blocks, given that only two social blocks from the control group met the criteria for inclusion in the matched performance analyses. Most importantly, across our new selection of blocks, there was no significant difference in performance between autistic and control participants on either the visual (p = 0.2935) or semantic (p = 0.2034) dimensions (Figure 3.15), thereby confirming that our selection of blocks achieved the goal of matching both participant groups on performance.

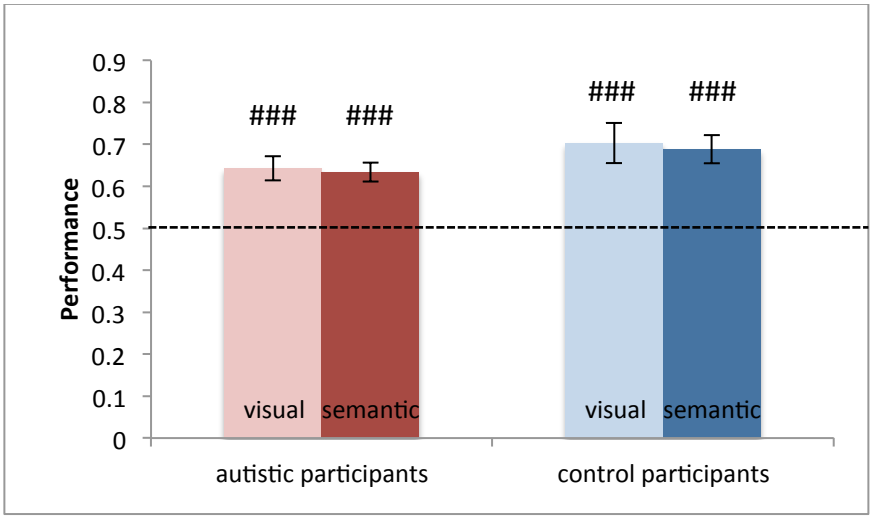


Figure 3.15. Mean learning performances across all blocks, for all participants, on blocks selected in order to best match performance across autistic participants and control participants. ### signifies p < 0.001. #'s are used for comparisons to 0.5.

We then computed the dimensional learning difference, the covariance between mean semantic performance and mean visual performance, and the correlation coefficient between mean semantic performance and mean visual performance, for both autistic and control participants, for the subset of blocks for which performance was matched across the two groups. Across autistic participants, the dimensional learning difference was 24.29%, the covariance was 0.0026, and the correlation coefficient was 0.0547, whereas these measures across control participants were 32.86%, -0.0170, and -0.3200, respectively.

We then randomized the order of blocks on each dimension, as described in Section 3.3, to generate null distributions for these quantities. Across the respective randomized distributions of block permutations for autistic participants, the mean dimensional learning difference was 24.85%, the covariance was ~0, and the correlation coefficient was 0.0008, whereas such measures across control participants were 28.86%, ~0, and -0.0007, respectively. As before, the absolute learning difference, covariance, and correlation were all within the 95% confidence interval of the respective randomized distributions of the autistic group ($p = 0.3828$, $p = 0.6640$, and $p = 0.6747$, respectively; Figures 3.16, 3.17, and 3.18). On the other hand, for the control group, while there was no significant difference between the true dimensional learning difference and the distribution of dimensional learning differences of the randomized blocks (Figure 3.19), the true covariance and correlation coefficients were both significantly outside the 95% confidence interval of the respective distributions of the randomized blocks (on the low- and high- ends, respectively; $p = 0.0030$ and $p = 0.0045$, respectively; Figures 3.20 and 3.21). We also compared the differences between the actual mean learning difference, covariance, and correlation coefficient of performance with respect to each dimension, to those values from the appropriate distributions of randomized blocks. As before, the difference between actual mean

dimensional learning difference for autistic participants and control participants was not significantly different from the difference between the randomized distributions of dimensional learning differences for autistic participants and control participants ($p \approx 1$). In contrast, the difference between actual mean covariance for autistic participants and control participants was significantly higher than the difference between the randomized distributions of covariance values for autistic participants and control participants ($p = 0.0180$). Furthermore, the difference between actual mean correlation coefficient for autistic participants and control participants was also significantly higher than the difference between the randomized distributions of correlation coefficients for autistic participants and control participants ($p = 0.0102$).

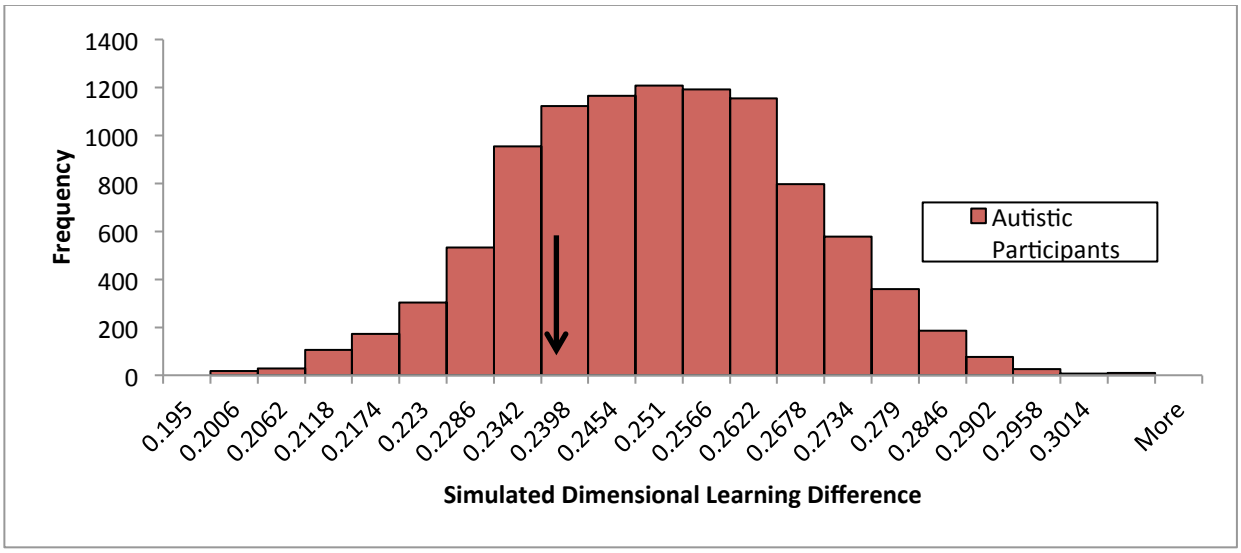


Figure 3.16. Distribution of the absolute differences between mean semantic performance and mean visual performance of autistic participants for 10,000 independent randomizations of block orderings, for blocks best matched on performance. The arrow indicates the actual difference.

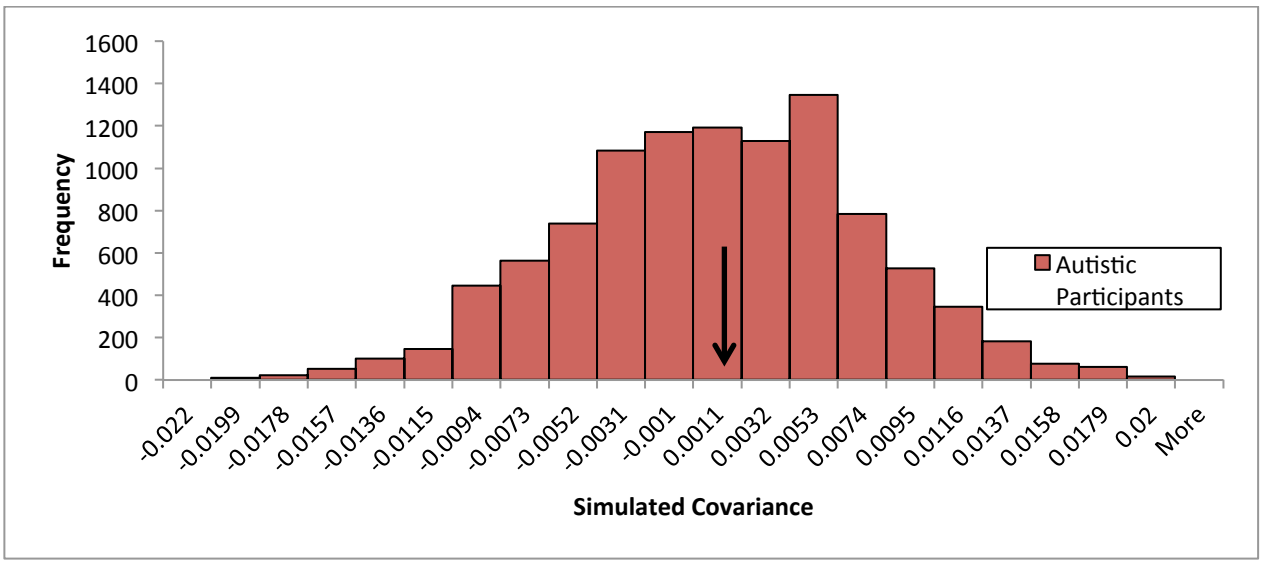


Figure 3.17. Distribution of the covariance values between mean semantic performance and mean visual performance of autistic participants for 10,000 independent randomizations of block orderings for blocks best matched on performance. The arrow indicates the actual covariance.

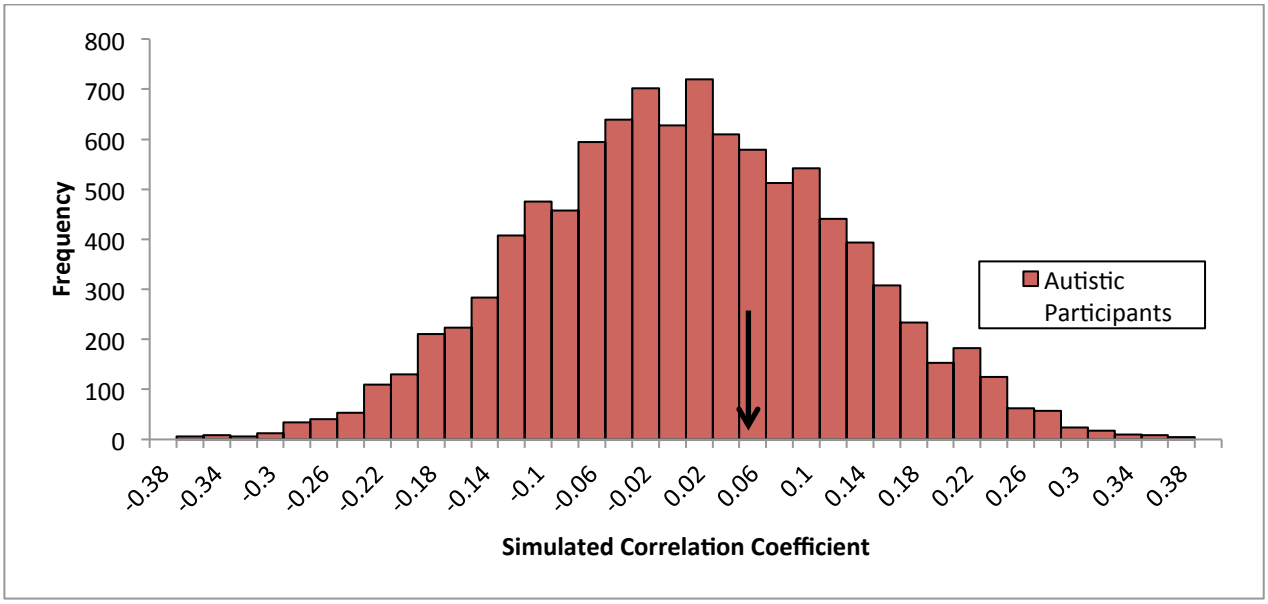


Figure 3.18. Distribution of the correlation coefficients between mean semantic performance and mean visual performance of autistic participants for 10,000 independent randomizations of block orderings, for blocks best matched on performance. The arrow indicates the actual correlation coefficient.

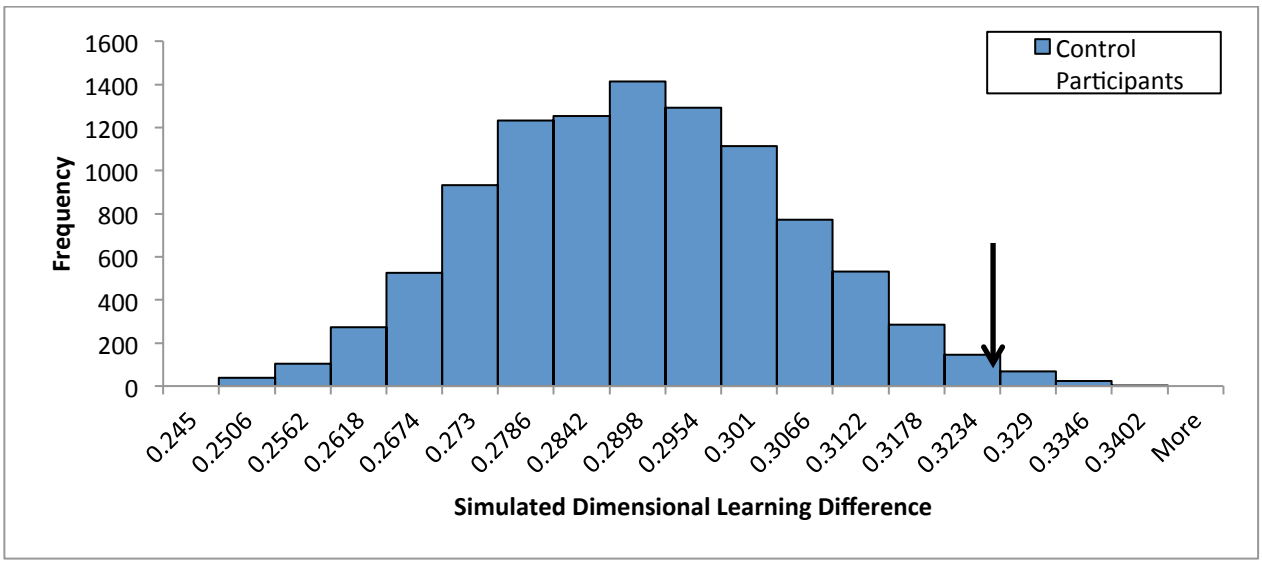


Figure 3.19. Distribution of the absolute differences between mean semantic performance and mean visual performance of control participants for 10,000 independent randomizations of block orderings, for blocks best matched on performance. The arrow indicates the actual difference.

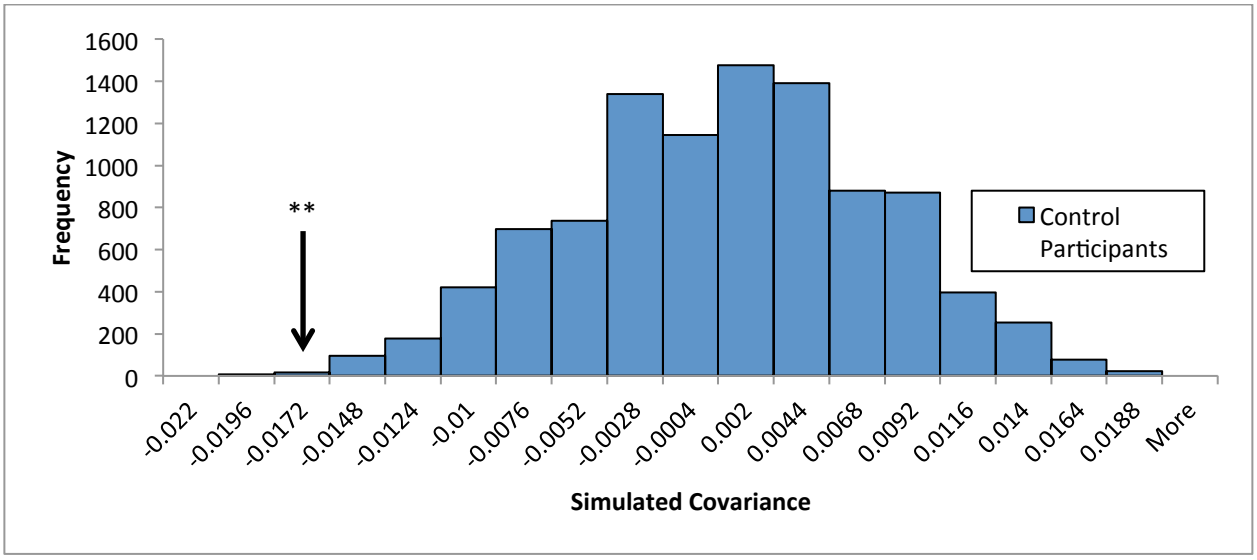


Figure 3.20. Distribution of covariance values between mean semantic performance and mean visual performance of control participants for 10,000 independent randomizations of block orderings, for blocks best matched on performance. The arrow indicates the actual covariance value. ** signifies $p < 0.01$.

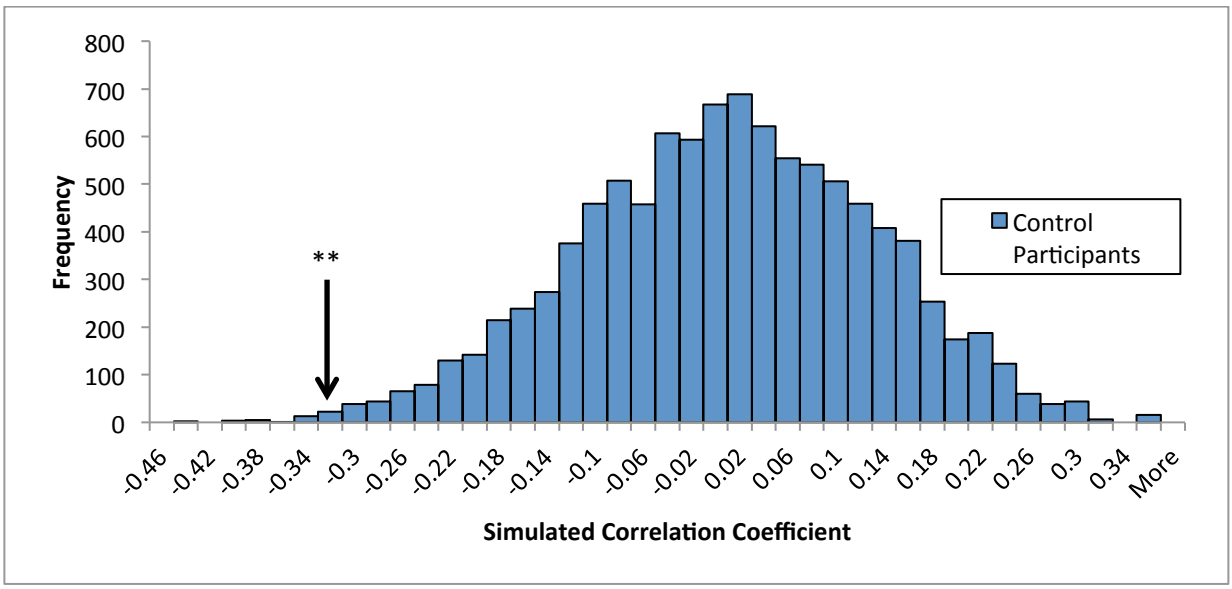


Figure 3.21. Distribution of correlation coefficients between mean semantic performance and mean visual performance of control participants for 10,000 independent randomizations of block orderings, for blocks best matched on performance. The arrow indicates the actual correlation coefficient value. ** signifies $p < 0.01$.

To summarize, control participants' visual and semantic performances appear to co-vary, a trend not observed across autistic participants, thereby suggesting the unanticipated conclusion that control participants might have a more narrow breadth of attention-based learning than autistic participants. These results directly contradicted our hypothesis, prompting us to perform additional analyses of the ILS questionnaires and of the pupillometry data described below in Sections 3.5 and 3.6, respectively, to further confirm, or possibly invalidate, these surprising findings.

3.5. Individualized Learning Style Questionnaire

Analyses of learning performance data can help infer one neural gain state versus the other, but in order to best clarify whether some participants exhibited characteristics of high or low gain, it is ideal to take into account individual predispositions of attention. That is, even if individuals in a state of high gain indeed attended to a single stimulus dimension, it is important

to consider whether this dimension is the one that the individual is most predisposed to learn from, as found in Eldar et al. (2013a). For this we used data from the ILS questionnaire.

The ILS questionnaire consists of a set of questions that allow us to infer participants' individual predispositions to learn from visual or semantic stimuli (Appendix A; Eldar et al., 2013a; Felder & Spurlin, 2005). Participants were each assigned an ILS score after completing the provided questionnaire (Appendix B), computed as described in Section 2.3. ILS scores range from 0 to 1, with values closer to 0 indicating an individual predisposition for learning from visual stimulus features, and with values closer to 1 indicating an individual predisposition for attending to semantic stimulus features.

Overall, control participants' ILS scores (mean ± SEM = 0.6364 ± 0.0813) were not significantly higher than scores for autistic participants' (mean ± SEM = 0.4545 ± 0.0359) although this difference did in fact approach significance ($p = 0.0557$). In other words, on the basis of responses to the ILS questionnaire alone, it appears that control participants were more predisposed to learn from semantic dimensions than autistic participants, and that autistic participants were more predisposed to lean from visual dimensions than control participants. That being said, ILS scores were not significantly different from 0.5 across both autistic participants ($p = 0.2367$) and control participants ($p = 0.1278$), suggesting that within each participant group, predispositions for stimulus dimensions varied across individual participants.

We expected individuals in the high neural gain state to exhibit a difference in semantic and learning performance that correlates with their respective ILS scores, whereas this association was expected to be weaker for those individuals in the low gain state (Eldar et al., 2013a). Therefore, we examined the association between dimensional learning differences and ILS scores, and found this correlation to be numerically positive but not significant across

autistic participants (R = 0.3730; p = 0.2884; Figure 3.22), and numerically negative but not significant across control participants (R = -0.1562; p = 0.6666; Figure 3.25). Moreover, across autistic participants, this correlation was relatively higher across social blocks (R = 0.4459; p = 0.1965) than across nonsocial blocks (R = 0.0884; p = 0.8080; Figure 3.27), whereas for control participants, this correlation was similar for both social (R = -0.1070; p = 0.7685) and nonsocial (R = -0.1632; p = 0.6524; Figure 3.26) blocks. Given that the correlation between the dimensional learning differences and ILS scores is expected to be stronger for individuals with high gain, these results certainly trend in the direction supporting our original hypothesis. That is, this correlation is stronger for autistic participants than control participants, indicating that autistic participants might be exhibiting higher gain. None of these correlations, however, were statistically significant, and so definitive conclusions cannot be drawn from these analyses.

We also examined the relationship between ILS score and learning performance, on only those blocks that qualified for the matched performance analyses described in Section 3.4, in order to compare this association in two groups that exhibit better homogeneity in terms of learning performance. We found the association between ILS scores and the differences of semantic performance and visual performance to be non-significant and numerically positive across both autistic (R = 0.3094; p = 0.3843) and control (R = 0.1216; p = 0.7378; Appendix D) participants, again inconclusive results.

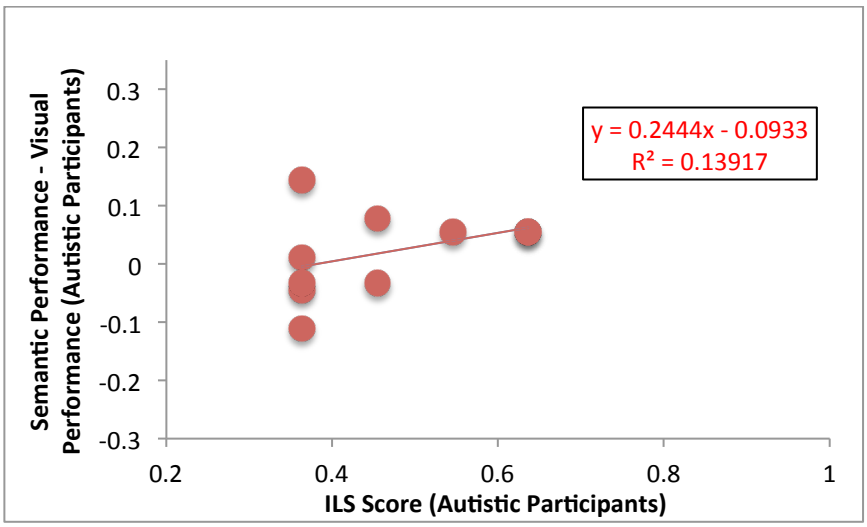


Figure 3.24. Association between ILS score and the difference between semantic performance and visual performance, across autistic participants.

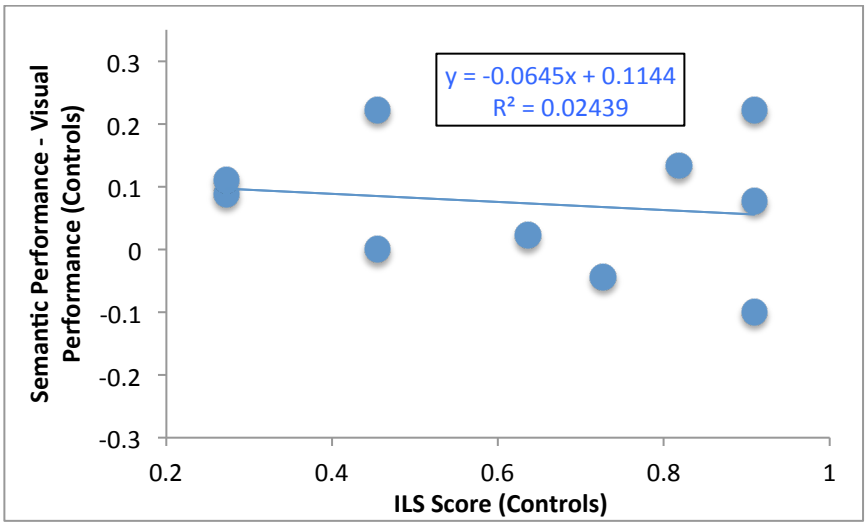


Figure 3.23. Association between ILS score and the difference between semantic performance and visual performance, across control participants.

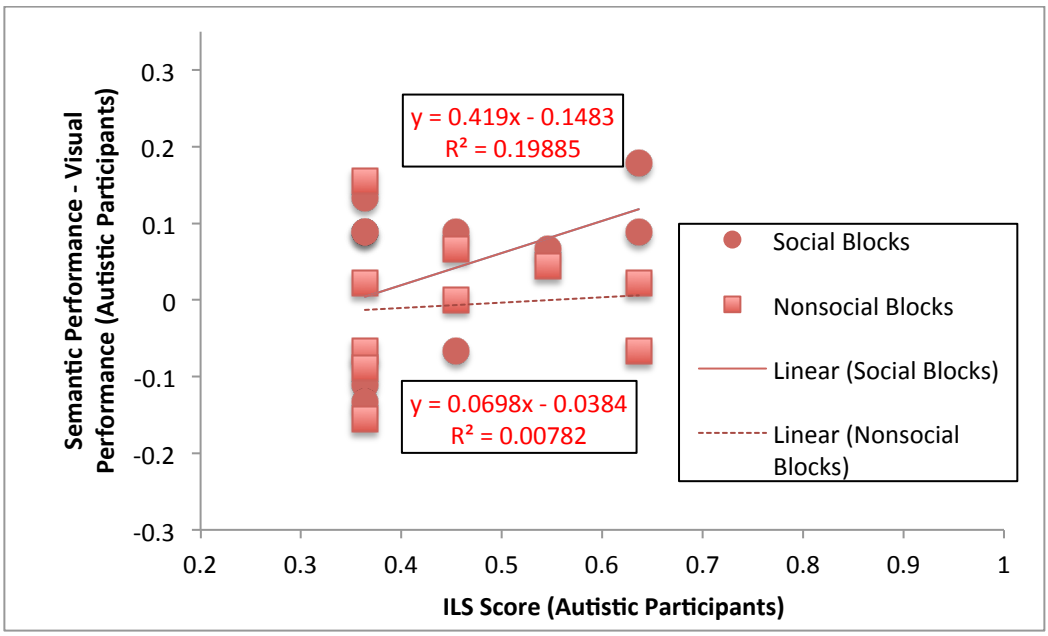


Figure 3.24. Association between ILS score and the difference in semantic performance and visual performance, across autistic participants, separated into social and nonsocial blocks. Equations and R-squared statistics refer to the nearest trend line.

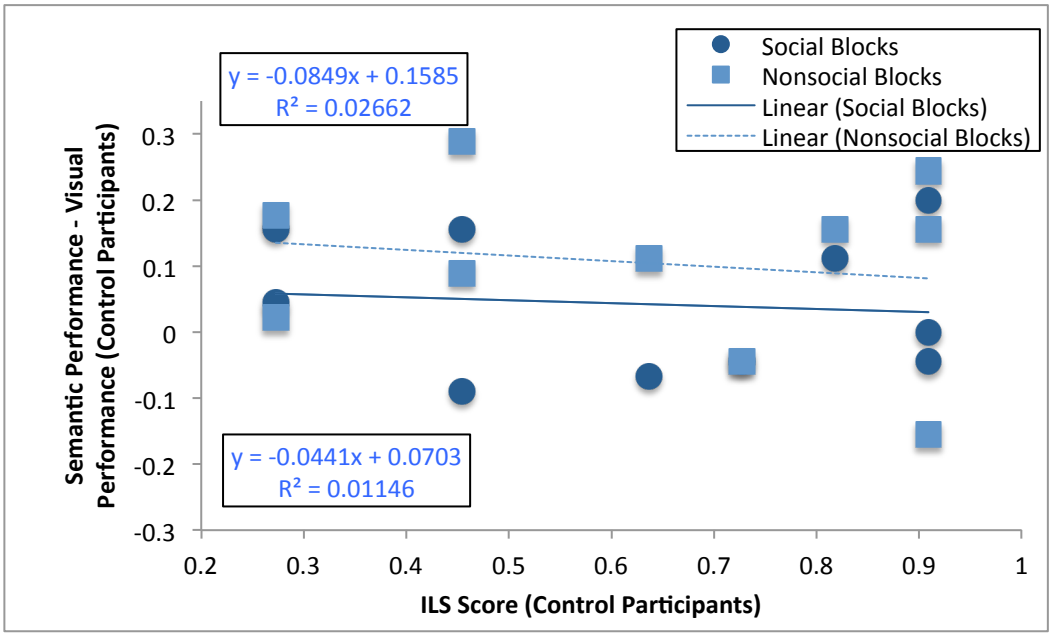


Figure 3.25. Association between ILS score and the difference in semantic performance and visual performance, across control participants, separated into social and nonsocial blocks. Equations and R-squared statistics refer to the nearest tread line.

3.6. Pupillometry

For each trial, we analyzed recorded pupil diameter data from the interval of time lasting from 1 s before stimulus presentation to 4 s after stimulus presentation, in order to have accurate representations of the baseline diameter for each trial, as well as to allow adequate time for pupil dilations to develop. Pupil diameters were normalized to the mean of the first second of data (prior to stimulus onset), and the data were smoothed as described in Section 2.4. The mean pupil diameter across all trials for each participant was computed for each sample interval (1/30 s), discarding artifacts as described in Section 2.4.

Given that the average pupillary response is expected to take approximately 2.5 s to reach its peak on the basis of the findings from Eldar et al. (2013a), we examined the pupillary responses during the first 3 s after stimulus presentation for each participant. For each trial we computed a pupillary response for each individual participant as the maximum diameter of the mean of pupil diameters across eyes, normalized to pre-trial baseline, across the aforementioned time interval. Mean post-stimulus pupil diameters were significantly higher than baseline for only 5 autistic participants and 6 control participants, indicating that the pupillometry data from the remaining participants were too noisy to be included in our analyses. (Noise would be expected for some participants, given that without a chinrest, some participants might have exhibited significant movements that caused pupillary responses to be overall undetected.) All below analyses thereby include only those participants for which mean pupillary diameters were significantly higher than baseline during the 3 s after stimulus presentation (Tables 3.4 and 3.5; Figure 3.28; Appendix E).

Overall, the pupillary responses across autistic participants (mean ± SEM = 104.30% ± 0.49%) were relatively lower than those across control participants (mean ± SEM = 106.34% ±

0.44%), although this difference was not statistically significant ($p = 0.1518$). We note that the lack of a significant difference in this comparison could likely be a consequence of the relatively small sample sizes of the two groups. In fact, we might not even expect to see an effect at all because some control participants are likely to be in a similar gain state as autistic participants (Eldar et al., 2013a). This is especially true given that only 1 control participant eligible for the pupillometry analysis had a positive covariance between visual performance and semantic performance, a behavioral indicator of low gain. Interestingly, as would be expected, this participant's maximum pupillary response (109.99%) was indeed significantly higher than the maximum pupillary responses across autistic participants ($p = 0.0003$), although it is clear that this analysis is also limited in its implications given the small sample sizes for comparison between the groups. Moreover, we might not expect to necessarily find a significant difference between two groups, if at least one member of a group can be anticipated to be similar to members of the other group. It is thus noteworthy that the pupillary responses for autistic participants were significantly lower than that of the five control participants with the highest pupillary responses among the six control participants ($p = 0.0100$), a noteworthy finding (albeit again limited by sample size) in light of the fact that of the control participants, we would expect those with higher mean pupillary responses to have relatively lower gain.

Thus, in summary, our data reveal that in general, autistic participants exhibited lower pupillary responses than control participants, lending evidence to the idea that autistic individuals' gain is higher than that of neurotypical individuals. Nevertheless, one might argue that given autistic individuals' deficient social development (Lai et al., 2014), our autistic participants might have exhibited overall lower pupillary responses than control participants because the social stimuli employed in the task did not induce emotional arousal in members of

the autistic group (Bradley, Miccoli, Escrig, & Lang, 2008). In light of this possibility, we compared pupillary responses between autistic participants and control participants, separately for social and nonsocial blocks. We found that across participants in each group, during social and nonsocial blocks, mean pupillary responses were significantly higher than baseline, for both the autistic ($p \approx 0$ for both) and control ($p \approx 0$ for both; Figure 3.27 and Figure 3.30) groups, in the first 3 s after stimulus presentation. That being said, on social blocks the pupillary response of the autistic participants did not gradually rise to an approximate single peak, thus suggesting that the autistic participants' pupillary responses might have indeed been affected by social stimuli. At the same time, across autistic participants, there were no significant differences between the pupillary responses across social (mean ± SEM = 107.39% ± 1.18%) and nonsocial (mean ± SEM = 105.42% ± 1.54%) blocks ($p = 0.1254$). Likewise, across control participants, there were no significant differences between the pupillary responses across social (mean ± SEM = 110.68% ± 2.75%) and nonsocial (110.41% ± 2.75%) blocks ($p = 0.9482$).

Autistic Participant	Pupillary Response (mean)	Difference from Baseline (p-value)
1	101.12%	~1
2	101.47%	0.9998
3	105.69%	0.0036
4	100.20%	~1
5	104.55%	~0
6	103.65%	0.7530
7	103.31%	~0
8	104.86%	~0
9	101.00%	~1
10	103.11%	~0

Table 3.4. Mean pupillary responses for autistic participants. Pupillary responses were calculated by normalizing pupil diameter measurements to the pretrial baseline diameter (the mean response in the second prior to stimulus onset), and then finding the maximum measurement in the first 3 s after stimulus presentation. One-tailed t-tests compared the range of values in this time interval to 100%. Cases in which this comparison is significant are indicated in green.

Control Participant	Pupillary Response (mean)	Difference from Baseline (p-value)
1	103.21%	0.1541
2	106.98%	~0
3	106.49%	~0
4	107.20%	~0
5	109.99%	~0
6	101.55%	~1
7	100.49%	~1
8	101.68%	~0
9	101.09%	~1
10	105.68%	~0

Table 3.5. Mean pupillary responses for control participants. Pupillary responses were calculated by normalizing pupil diameter measurements to the pretrial baseline diameter (the mean response in the second prior to stimulus onset), and then finding the maximum measurement in the first 3 s after stimulus presentation. One-tailed t-tests compared the range of values in this time interval to 100%. Cases in which this comparison is significant are indicated in green.

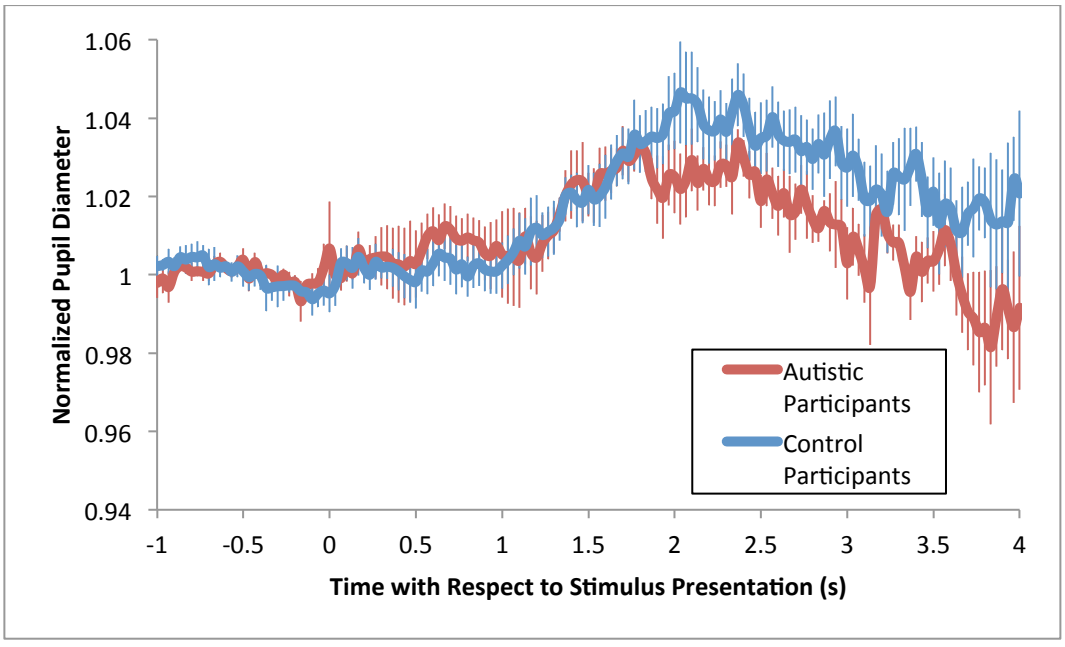


Figure 3.28. Mean pupillary response to stimulus presentation across trials, averaged across participants. Pupil diameter was normalized to the mean of recordings in the second before stimulus presentation.

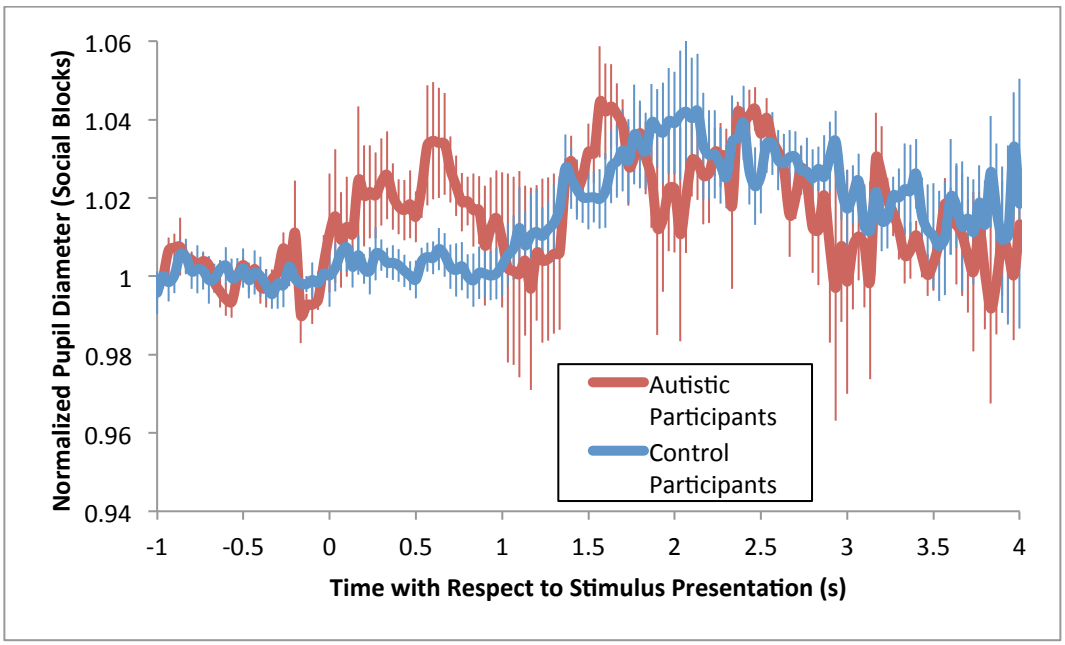


Figure 3.29. Mean pupillary response to stimulus presentation across trials during social blocks, averaged across participants. Pupil diameter was normalized to the mean of recordings in the second before stimulus presentation.

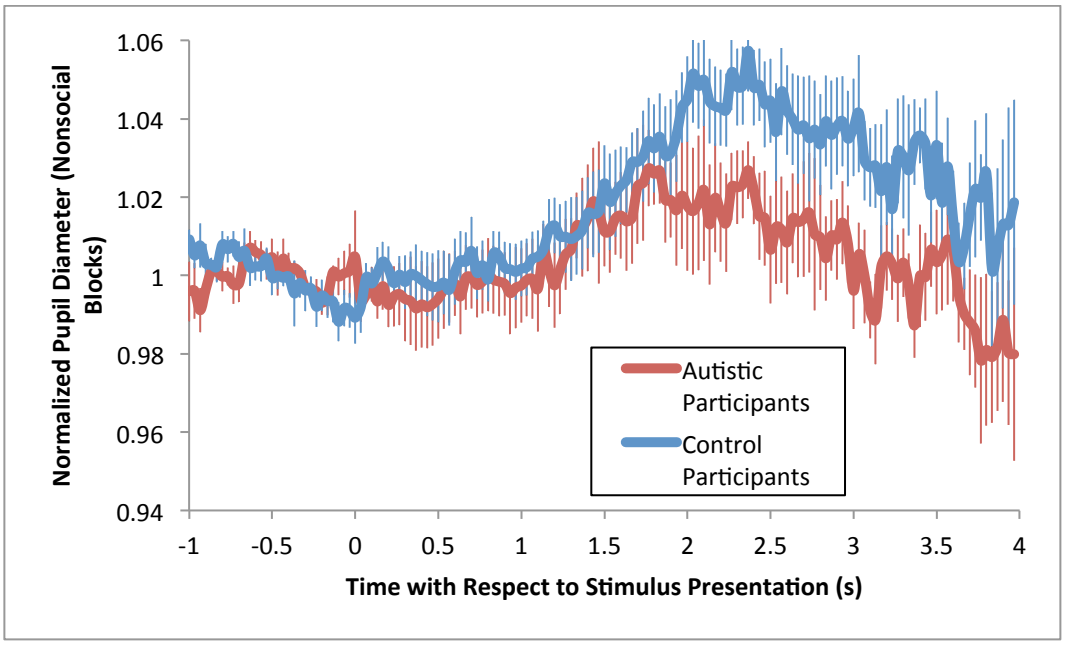


Figure 3.28. Mean pupillary response to stimulus presentation across trials during nonsocial blocks, averaged across participants. Pupil diameter was normalized to the mean of recordings in the second before stimulus presentation.

Again, the maximum pupillary responses across autistic participants were significantly lower than that of the 1 control participant exhibiting learning behaviors characteristic of the low gain state again across both social ($p = 0.0153$) and nonsocial ($p = 0.0007$) blocks. However, there were no significant differences between autistic participants' pupillary responses and those of the 5 control participants with the lowest gain (as determined by pupillary responses), across both social ($p = 0.6827$) and nonsocial ($p = 0.1581$) blocks. This could likely have been a consequence of reduced sample size, when comparing social and nonsocial blocks separately. Alternatively, this could have resulted from the fact that pupillary responses to social stimuli (Bradley et al., 2008) concealed the effect, given the trend toward a significance difference in pupillary responses between autistic and control participants across nonsocial—but not social—blocks. Either way, separate comparisons of pupillary responses across social and nonsocial blocks likely does not invalidate our aforementioned findings from analyzing data pooled across both block types, particularly given that differences between pupillary responses across social and nonsocial blocks were non-significant for both participant groups. Based on these analyses, we thereby conclude that our group comparison results are unlikely to reflect group differences in pupillary responses to social versus nonsocial stimuli.

Given the reported association between successful performance on a single, predisposed dimension and exhibition of the high neural gain state (Eldar et al., 2013a), we examined the association between mean pupillary response and the three measures that would be expected to differ in individuals in the high gain state versus those in the low gain state: the absolute difference, covariance, and correlation between semantic performance and visual performance. A non-significant negative correlation between pupillary response and the dimensional learning difference was found across both autistic participants ($R = -0.0385$; $p = 0.9510$) and control

participants (R = -0.4017; p = 0.4299; Figure 3.30). Furthermore, there was a non-significant positive correlation between pupillary response and the covariance of visual performance and semantic performance across autistic participants (R = 0.7620; p = 0.1343), and this correlation was non-significant and negative across control participants (R = -0.2009; p = 0.7027; Figure 3.29). In addition, there was a non-significant positive correlation between pupillary response and the correlation coefficient of visual performance and semantic performance across autistic participants (R = 0.7979; p = 0.1057), and this correlation was non-significant and negative across control participants (R = -0.1575; p = 0.7657; Figure 3.32). Moreover, pooling data together from autistic participants and control participants, there were non-significant negative correlations between pupillary response and the absolute difference, covariance, and correlation between visual performance and semantic performance (R = -0.3290, -0.2327, and -0.2295, respectively; p = 0.3232, 0.4911, and 0.4973, respectively). We would expect that if indeed our behavioral measures correspond with our pupillometry recordings, that all aforementioned correlations would be positive in both groups. However, these analyses do not discount our experimental design given that none of the above correlations were significant, and so greater statistical power before being able to draw any conclusions from these specific correlations.

In light of the fact that none of the aforementioned correlations were significant, we proceeded to test the association between pupillary response with the correlation of ILS score and task performance, as described by Eldar et al. (2013a). Participants were divided into two groups on the basis of their respective pupillary responses. That is, the 5 participants with the lowest five mean pupillary responses were each placed in one bin, while the remaining 6 participants were each placed in another. For participants with lower mean pupillary responses and for those with higher mean pupillary responses, the correlations between ILS scores and

dimensional learning performance difference were non-significant and positive in both cases (R = 0.6403 and 0.0046, respectively; p = 0.2445 and 0.9931, respectively). At the same time, the correlation between mean pupillary responses and the association between ILS scores and dimensional learning performance, for each bin, appears to be an inverse relationship, consistent with the results from Eldar et al. (2013a). Overall, given the lack of significance in the aforementioned regression analyses, we cannot draw definitive conclusions regarding pupillary responses' relationship to learning behaviors in our task. The fact that Eldar et al. (2013a) were able to find such significant correlations among a neurotypical sample, but we could not, suggests that we might not be seeing such any effects in the aforementioned analyses due to our relative lack of statistical power.

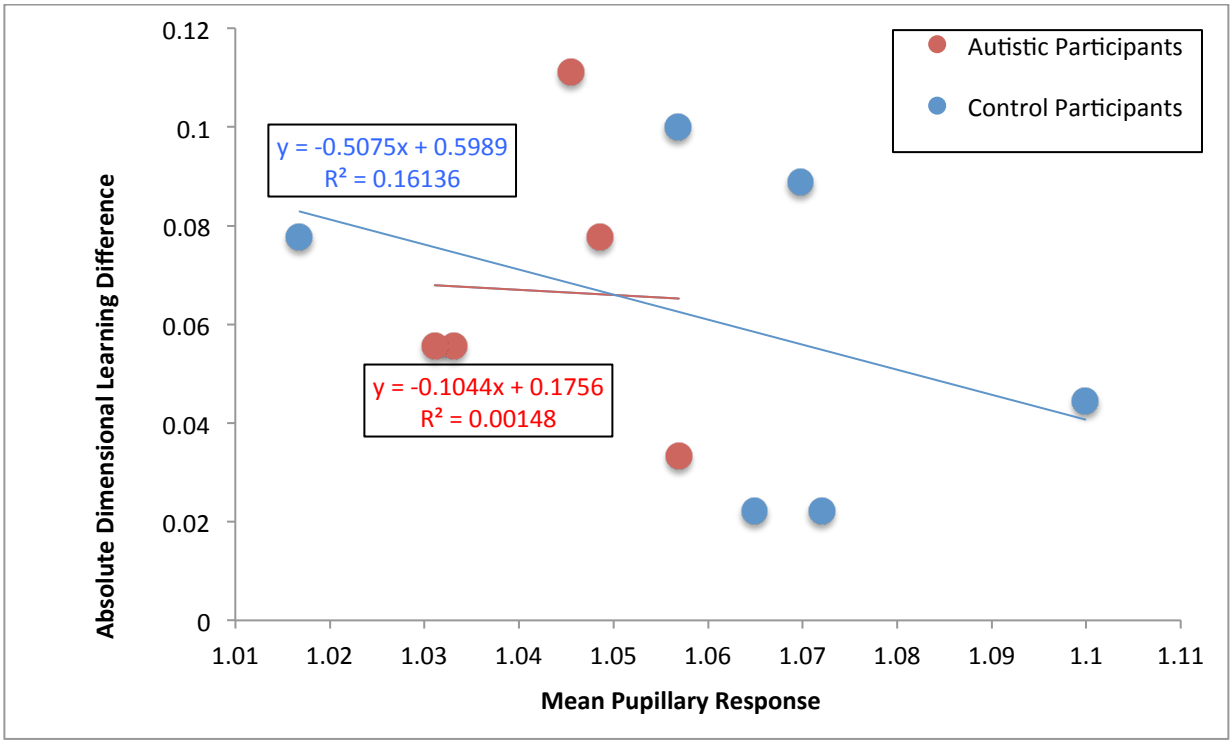


Figure 3.30. Association between pupillary response and the absolute difference of semantic performance and visual performance, across autistic participants and control participants.

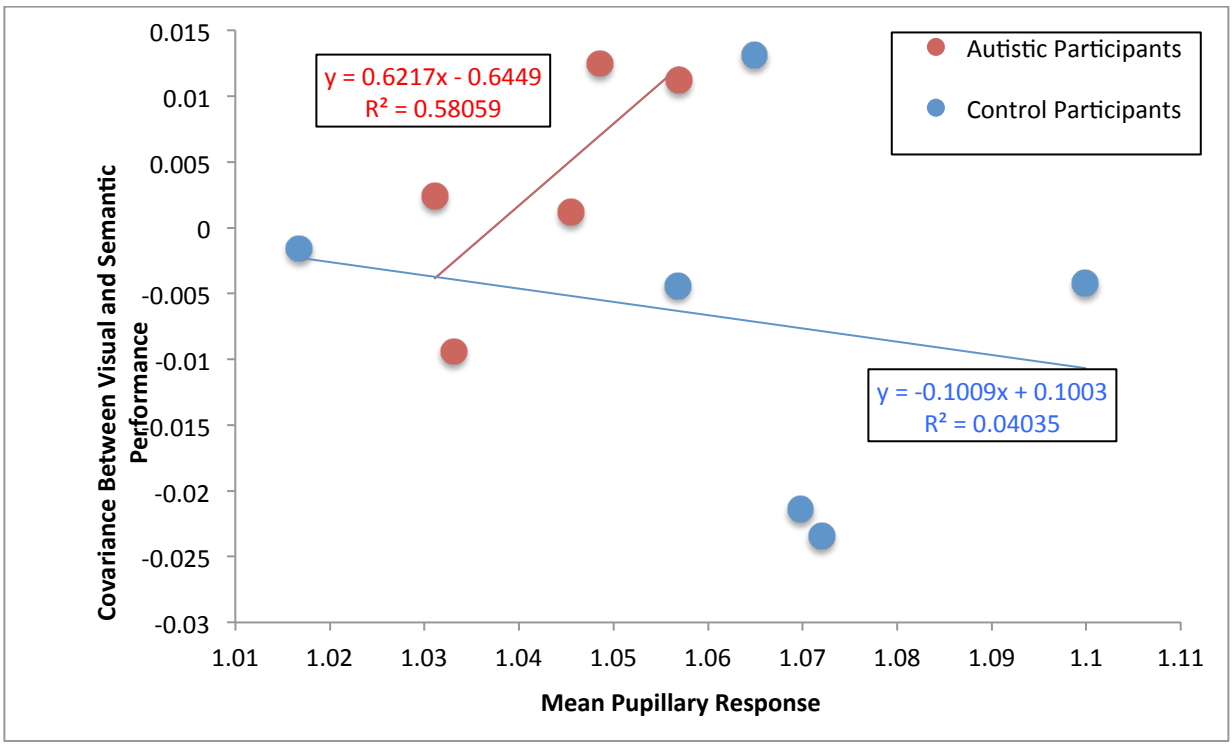


Figure 3.31. Association between pupillary response and the covariance between visual performance and semantic performance, across autistic participants and control participants.

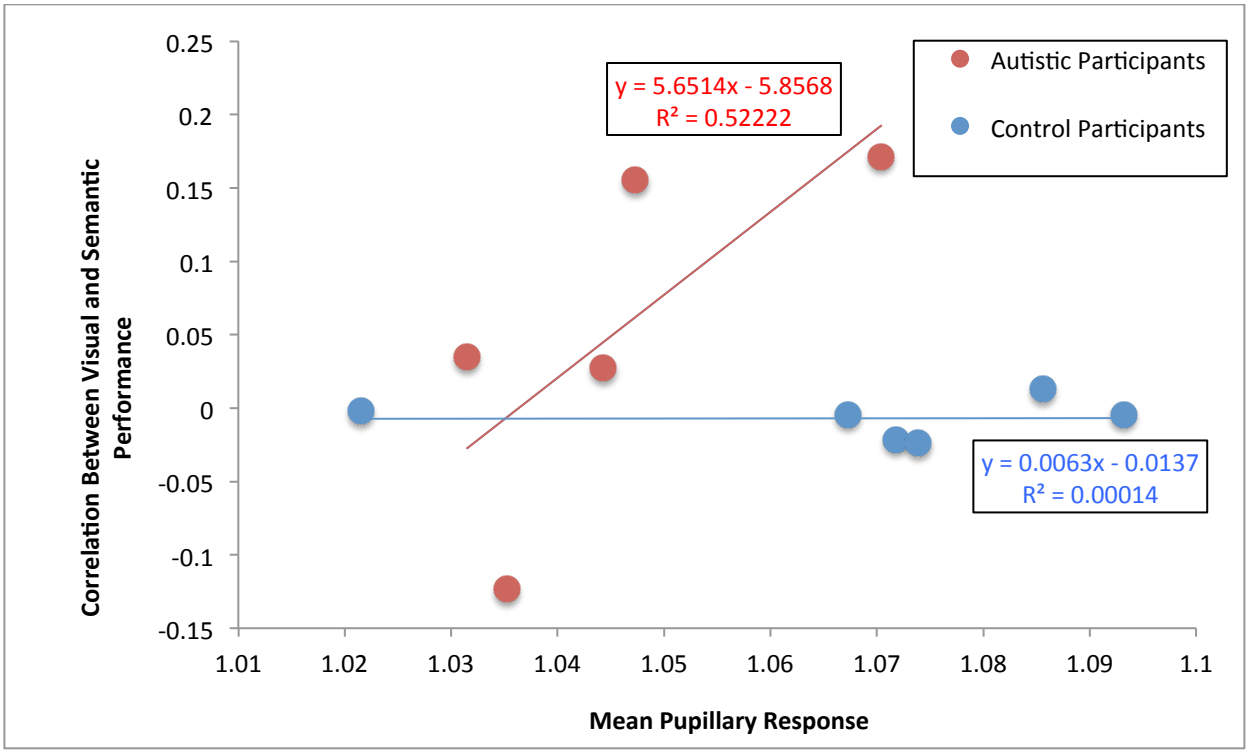


Figure 3.30. Association between pupillary response and the correlation coefficient between visual performance and semantic performance, across autistic participants and control participants.

Chapter 4

Discussion

The purpose of this thesis was to test the hypothesis that individuals with autism are constitutively in a state of high gain. We formulated this hypothesis primarily because autistic individuals exhibit elevated baseline pupil sizes compared to neurotypical controls (Anderson & Colombo, 2009), and neurotypical individuals with increased pupil sizes are shown to have high gain (Eldar et al., 2013a). To test our hypothesis, we compared the performance of autistic and neurotypical participants on a multidimensional learning task, while also recording their respective pupillary responses.

In spite of the relatively low sample sizes for each group due to restricted autistic participant availability, the results presented in Chapter 3 offer tentative evidence for two conceivable—albeit at first apparently conflicting—observations that might allow us to explain a neural basis for autistic attention-based learning behaviors. In this discussion, we will first rationalize the possibility of our initial hypothesis, that individuals with autism are constitutively in a state of high neural gain. We will then consider and offer support for an alternative conclusion, that individuals with autism might constitutively exhibit behaviors consistent with the low neural gain state, a theory that is indeed consistent with our complete results and will thereby be justified below.

4.1. Autistic Group Analyses: Consistencies with High Neural Gain?

We will first evaluate the possibility that our original hypothesis indeed might stand true: that is, that individuals with autism might constitutively be in a state of high neural gain, unlike neurotypical individuals who can be in states of low or high gain in various contexts (Eldar et al.,

2013a). Comparisons of visual and semantic performances between autistic and control participants revealed that control participants had significantly better learning performance on both the visual and semantic dimensions. Control participants also had greater learning performance (approaching significance) on the semantic dimension than on the visual dimension, a trend not observed in the autistic group (Figure 3.4). Control participants' superior semantic performance compared to their visual performance, was expected on this task, as such results would be consistent with previous findings in a similar experimental design (Eldar et al., 2013a). We can thereby assume that had our sample size been larger, the difference in visual and semantic performances across control participants might have reached statistical significance.

That being said, from this information alone, we cannot definitively assert that autistic participants' learning behaviors actually differed significantly from control participants': given that autistic individuals are believed to be predisposed to attend to visual environmental features (O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001), and that semantic learning is expected to be generally easier than visual learning on our task (Eldar et al., 2013a), it should not be surprising that there is no significant difference in visual and semantic performances across autistic participants. In fact, this lack of an effect might be irrelevant to our hypothesis and might simply suggest that autistic individuals found the experimental task to be more challenging, as compared to control participants. We thus ran two simulations of our task: one that assumed that autistic participants would only be attending to a single stimulus dimension or another (a behavioral indicator of high gain; Eldar et al., 2013a; Figure 3.6), and another that assumed that autistic participants might be attending either to one stimulus dimension or both (a behavioral indicator of low gain; Eldar et al., 2013a; Figure 3.7), while simply learning less effectively about the dimensions that they were attending to. Each simulation generated trends in learning

that were consistent with our actual data, thereby suggesting that this set of experimental results cannot be used to either prove or disprove our original hypothesis.

Given that individuals with high gain should have visual and semantic performances that inversely co-vary with one another (that is, selective attention to one dimension, and not to both; Eldar et al., 2013a), we next conducted several permutation tests to determine whether performances on the two dimensions were in fact associated with one another. For both groups, we found that the dimensional learning difference, covariance between mean semantic performance and mean visual performance, and correlation coefficient between mean semantic performance and mean visual performance were all within a 95% confidence interval of respective sampling distributions of these values generated under the assumption that visual performance and semantic performance were independent from one another (Figures 3.8, 3.9, 3.10, 3.11, 3.12, and 3.13). In other words, we were unable to establish that visual performance and semantic performance co-varied with one another across either autistic or control participants, and most importantly, there was no significant difference in the covariance of performance on the two dimensions between the autistic and control groups. The lack of a difference between groups might be a consequence of the fact that there are general differences in the level of difficulty of the task between the two groups. That is, we cannot compare each group's learning styles given the general effect on learning.

As we could not make inferences pertinent to an individual's gain state from the performance data alone, we proceeded to examine the association between individual predispositions to stimuli and differences in semantic versus visual performance, given that the correlation between ILS scores and the difference in semantic versus visual performance is expected to be significantly stronger across individuals with high gain, as compared to those with

low gain (Eldar et al., 2013a). While this correlation was not statistically significant for either autistic or control participants in our study (possibly because of small sample sizes), the correlation was relatively stronger across autistic participants (Figures 3.22 and 3.23), than across control participants. It is thus conceivable that with more statistical power, we might see these trends approach significance, which would support the idea that autistic participants are indeed constitutively in a state of high neural gain. That being said, we cannot make such a conclusion without running additional participants on our task.

Finally, pupillometry can be used to infer neural gain state in light of the documented associations between LC activity, task performance, and pupil size (Aston-Jones et al., 1994; Gilzenrat et al., 2010), in addition to the demonstrated inverse correlation between baseline pupil diameter and pupillary response (Eldar et al., 2013a; Gilzenrat et al., 2010). It is thus noteworthy that the pupillary responses across autistic participants were relatively lower than those across control participants. The lack of a statistically significant difference between the two groups on this measurement is not surprising given that one group consisted of 5 participants, whereas the other contained 6. That being said, even with more participants, we might not expect to find a statistically significant difference between these groups because the control group can theoretically include individuals with approximately the same gain as autistic participants, assuming our original hypothesis. In fact, visual performance and semantic performance negatively co-varied for all but 1 control participant, a potential behavioral indicator that all but 1 control were also conceivably in a state of high gain. Indeed when excluding the mean pupillary response of the 1 control with the smallest dilation (suggestive that this individual was exhibiting high gain; Eldar et al., 2013a), we find that the mean pupillary responses across autistic participants were indeed significantly lower than those across control participants. Therefore,

despite the few conclusions that can be made from the behavioral data, our pupillometry results offer clearer support for the possibility that autistic participants might be constitutively in a state of high neural gain. That being said, because our current analyses fail to show the expected significant relationships between pupillary responses and learning performances (Figures 3.26, 3.27, and 3.28), data from more participants might be necessary to confirm or disprove this conclusion.

One might argue with our approach to analyzing the pupillometry data by noting that across our control participants, there is also a discrepancy between pupillary responses (which appear to signify low gain) and learning performances (which appear to signify high gain). However, it is important to note that only 1 control participant (out of the 6 eligible for our pupillometry analyses; Chapter 3) exhibited behaviors consistent with the low neural gain state, and that this control exhibited the highest pupillary response. That is, all other control participants had lower pupillary responses than the control participant exhibiting behaviors consistent with low gain, and so it is reasonable that the remaining control participants could exhibit behaviors consistent with high gain. Gain is indeed relative and on a spectrum: we are not arguing that control participants with pupillary responses higher than autistic participants' are necessarily in a state of low gain. Instead, we suggest that these control participants have apparently lower gain (as measured by pupillary responses) than the autistic participants, but not necessarily lower gain than other control participants. In fact, this might be expected. It is likely that many (if not all) of the participants in our study had never previously participated in a research investigation, and so the situation probably induces a relatively significant extent of stress in participants. As stress can increase NE production and neural gain (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007), it is conceivable that all of our participants had temporarily

high gain in our experiment. That being said, given that autistic individuals generally exhibit excessive anxiety in unfamiliar situations (Lai et al., 2014), we might anticipate that autistic participants have an even higher increase in gain, as compared to control participants, a possibility that is indeed consistent with the aforementioned group difference in pupillary responses.

4.2. Autistic Group Analyses: Consistencies with Low Neural Gain?

The second possibility that we would like to entertain, in light of our data, is that autistic participants in our study exhibited a wider attentional breadth when learning from multidimensional stimuli compared to the control participants, contrary to our initial hypothesis. This potential conclusion arises from our series of analyses in which autistic participants and control participants were matched on performance (as described in Section 3.4), a procedure meant to allow us to compare learning styles between autistic and control participants, while eliminating the main effect of general learning differences between the two groups.

In our analyses of the matched data, we found that while neither the covariance nor the correlation coefficient between semantic performance and visual performance for autistic participants were outside a 95% confidence interval of sampling distributions of these respective values generated under the assumption that semantic performance and visual performance were independent from one another, the covariance and correlation coefficient for control participants were in fact outside this interval. That is, there was significantly stronger negative covariance between visual performance and semantic performance across control participants, than expected under the null hypothesis, but this was not true for autistic participants. These analyses thereby suggest that the control participants appeared to exhibit behavioral characteristics that could be associated with high neural gain, whereas autistic participants appeared to exhibit behavioral

features that could be associated with low neural gain, evidence against our original hypothesis claiming that autistic individuals are constitutively in the high gain state. Given that the permutation tests underlying this conclusion are statistically significant, and that the behavioral analyses (examining the association between ILS scores and semantic versus visual performance) supporting our original hypothesis are not, we will argue below for an alternative proposal to explain why autistic learning behaviors observed in our task might resemble those of an individual with low gain.

4.3. A Proposal for Neural Gain's Contributions to Autism

Our study revealed two statistically significant and scientifically relevant effects: (1) mean pupillary responses are significantly lower for autistic participants than for control participants (after removal of data from a control participant who was likely in a state of high neural gain), and (2) visual performance and semantic performance co-vary significantly more across control participants than across autistic participants. That is, interestingly, autistic participants appeared to be exhibiting *physiological* features consistent with higher gain than control participants and *behavioral* characteristics consistent with lower gain than control participants. We offer a cohesive model that is consistent with both the fact that autistic participants exhibited pupillary responses indicative of high gain and learning behaviors indicative of low gain, which first necessitates a discussion of adrenergic receptors that are innervated by the LC. Specifically, we propose that hyperactivity of the LC induces a down-regulation of noradrenergic receptors in the cortex of autistic individuals, and that autistic individuals nonetheless exhibit elevated baseline pupil sizes because adrenergic receptors governing pupillary responses are not readily desensitized.

As outlined in Chapter 1, neural gain refers to the ability of the brain to modulate the intensity of neural input. In the high neural gain state, LC activity is up-regulated, stimulating the release of NE globally throughout the brain, and thereby enhancing the activation of excitatory neurons and lowering the activation of inhibitory neurons (Aston-Jones & Cohen, 2005). Pupillometry is a useful correlate of LC activity given that the Endinger-Westphal nucleus (EWN; the region of cells that modulate the ganglia controlling ciliary muscle) receives input from the LC. When NE binds to adrenergic receptors in EWN cells, these neurons are inhibited, thereby down-regulating output to the ganglia governing ciliary muscle, and consequently resulting in pupil dilation. On the other hand, when less NE is present in the synaptic cleft of EWN presynaptic cells, these neurons are more readily activated and can excite ciliary muscle ganglia in order to constrict the pupil (Samuels & Szabadi, 2008).

It is likely that the LC-NE system has such a broad range of effects on physiology and behavior not only as a consequence of the range of its projections (Figure 1.1; Aston-Jones & Cohen, 2005), but also given NE's broad range of receptor targets (Samuels & Szabadi, 2008). That is, LC activity can have a variety of effects in different regions of the brain that are dependent on the noradrenergic receptors in each area. NE typically has an affinity for one of the five primary classes of adrenergic receptors: α_1, α_2, β_1, β_2, and β_3 (Kandel, Schwartz, & Jessell, 2000). NE released from the LC binds to all such receptors: activation of the α_2-adrenergic receptor generally results in inhibition, whereas activation of the other classes of adrenergic receptor typically results in excitation (Samuels & Szabadi, 2008).

Differences in adrenergic receptor expression and pharmacokinetics might be able to account for the apparent discrepancies between the autistic participants' relatively low pupillary responses (a physiological indicator of high gain; Eldar et al., 2013a) and attention to multiple

stimulus dimensions (a behavioral indicator of low gain; Eldar et al., 2013a). Pupillary response is dictated by the activation of α_2-adrenergic receptors in the EWN. α_2-adrenergic receptors can be further categorized into multiple classes in humans: α_{2A}, $\alpha_{2B,}$ and α_{2C}. An α_{2A}-adrenergic receptor orthologue is found in the homologous EWN region in mice (Docherty, 1998; Heal et al., 1995; Samuels & Szabadi, 2008), suggesting that the EWN in humans likely consists of α_{2A}-adrenergic receptors, as do other nuclei proximal to EWN (Wang et al., 1996). Importantly, the half-maximal concentration required for α_{2A}-adrenergic receptor down-regulation is approximately 20 times greater than that for the α_{2B}- and α_{2C}-adrenergic receptors (Heck & Bylund, 1998), and NE needs to bind at a 100-fold greater rate to α_{2A}-adrenergic receptor than to α_{2B}- or α_{2C}-adrenergic receptors, in order to achieve equivalent extents of receptor down-regulation (Heck & Bylund, 1997). That is, α_{2A}-adrenergic receptor, which is likely involved in modulating pupillary response, is not readily desensitized at moderate physiological concentrations of NE. This suggests that we might expect to observe an elevated baseline pupil size (and a consequent relatively low pupillary response) even in individuals with chronic NE release, support for the idea that the relatively low mean pupillary response measured across our autistic participants could indeed be a consequence of an up-regulation of the LC-NE system.

In contrast to the α_{2A}-adrenergic receptor, other adrenergic receptors that are expressed throughout the brain are readily desensitized at sufficient NE concentrations. For instance, the α_{2C}-adrenergic receptor—the receptor most readily desensitized among the α_2-adrenergic receptor family (Bücheler, Hadamek, & Hein, 2002; Eason & Liggett, 1992)—has been implicated in inhibiting sensory processing (Philipp, Brede, & Hein, 2002). The α_{2C}-adrenergic receptor is also heavily expressed in the amygdaloidal complex, olfactory system, hippocampal region, cerebral cortex, and basal ganglia (Wang et al., 1996). The α_{2B}-adrenergic receptor, also

readily desensitized (Nguyen, Kassimatis, & Lymperopoulos, 2011), is heavily expressed in the thalamus (Wang et al., 1996). Thus, if autistic individuals are chronically generating heightened concentrations of NE, α_2-adrenergic receptors throughout their brains might ultimately become desensitized to the presence of NE (Figure 4.1), consequently releasing neurons in these regions from inhibition that would normally be the consequence of α_2-adrenergic receptor activity (Samuels & Szabadi, 2008). This could explain why autistic individuals are hypersensitive to environmental stimuli (Lai et al., 2014).

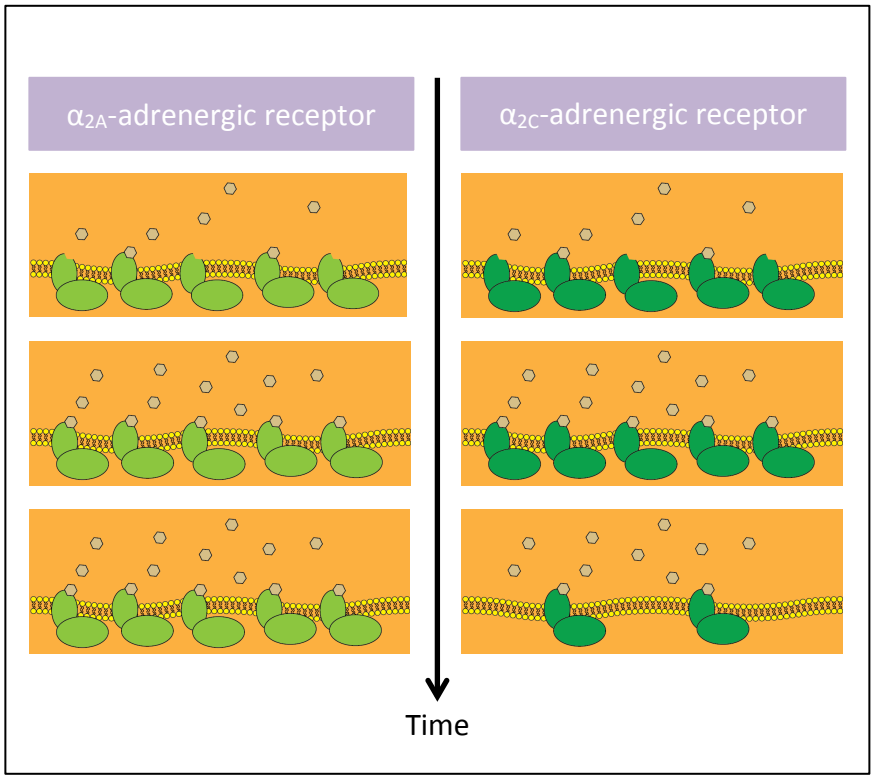


Figure 4.1. Comparison of chronological long-term effects of constitutive NE release on adrenergic receptor surface expression for different types of adrenergic receptors, as posited by Heck & Bylund (1997). α_{2A}-adrenergic receptors maintain steady-state surface expression concentrations over time, whereas α_{2C}-adrenergic receptors ultimately degrade.

While inhibitory neurons will be disinhibited after desensitization of α_2-adrenergic receptors, excitatory neurons with other classes of adrenergic receptors in the brain are also susceptible to desensitization of neural input (Hausdorff, Caron, & Lefkowitz, 1990; January et al., 1997; Lohse, Benovic, Caron, & Lefkowitz, 1990; Rainbow, Parsons, & Wolfe, 1984). Thus, we would not only anticipate that chronic release of NE would consequently disinhibit inhibitory neurons, but also down-regulate excitatory neurons. In other words, theoretically speaking, gain would be largely diminished, and there would be fewer means to distinguish neural input's effects on neural output in either "excitatory" or "inhibitory" neurons (Figure 4.2).

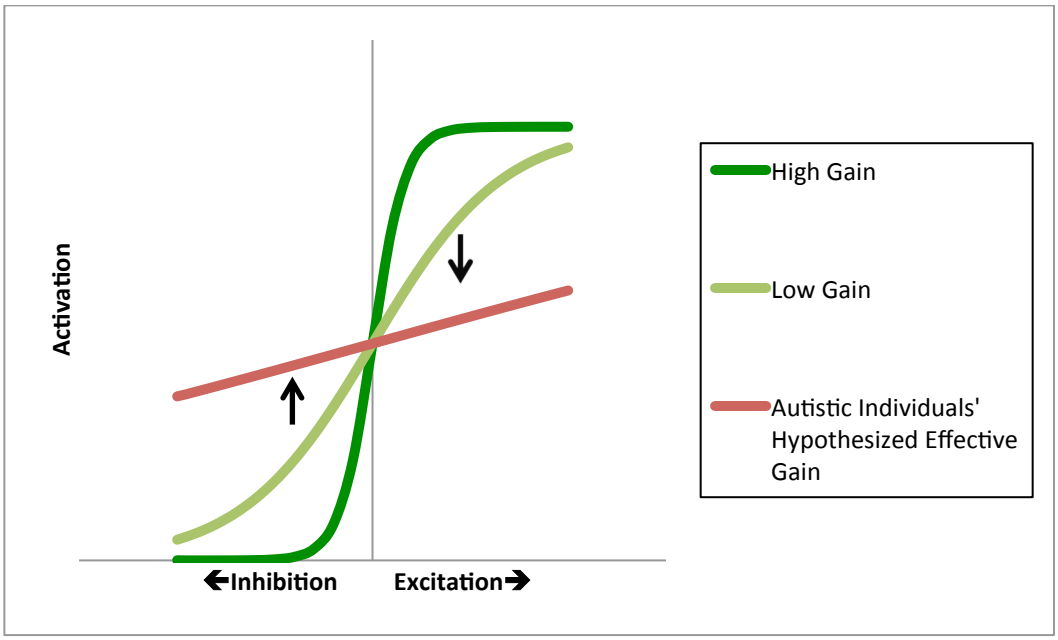


Figure 4.2. Our proposal for the effects of chronic NE release on neural gain. Our proposed model of neural activity in autistic individuals suggests that autistic individuals have an effective low gain state despite, and due to, their chronically elevated LC-NE activity.

Given that the desensitization to NE might occur in areas of the brain involved in sensory and cognitive processing, as well as decision-making, an individual with chronically elevated NE concentrations might therefore exhibit learning patterns characteristic of low neural gain. Thus, the original model of neural gain's effects on both physiology and behavior demonstrated by

Eldar et al. (2013a) might not strictly apply to individuals with autism. We propose that in autistic individuals, tonic LC activity might result in a global and chronic up-regulation of NE, consequently causing relatively low pupillary responses (given that the α_{2A}-adrenergic receptor in the EWN is not readily desensitized; Heck & Bylund, 1997) alongside desensitization of NE receptor and thus, effectively, *lower* neural gain throughout the brain.

Autistic individuals might have significantly lower gain than even most neurotypical individuals exhibiting features of low gain, as adrenergic receptor surface expression lessens. Not only would gain be decreased, but the dynamic range, or the ability of the LC to modulate gain, would also be diminished. That is, the concentration of NE released from the LC would have minimal influence over the activation of neural circuits, globally throughout the brain. In the case of such a perpetual low gain state, an individual might rarely exploit information from his environment, but rather would be constantly exploring, thereby limiting the acquisition of priors and hindering reward-based learning. Notably, the locus coeruleus exhibits phasic activity during instances of unexpected uncertainty (Payzan-LeNestour, Dunne, Bossaerts, & O'Doherty, 2013). Thus, it is possible that autistic individuals, whose neural circuits might not be affected by changes in NE concentrations, could constitutively be in a state of unexpected uncertainty when interacting with the environment. Viewing autistic features as a consequence of such chronic unexpected uncertainty will be further explored below.

4.4. Our Proposed Model's Consistencies with Autistic Features

Given the established inverse correlation between pupil diameter and pupillary response, our results are consistent with the previously reported findings that autistic individuals exhibit higher baseline pupil sizes, in comparison to a neurotypical population (Anderson & Colombo, 2009). Our results also aid to resolve the debate over whether individuals with autism have

difficulty disengaging from stimuli in their environments, thereby resulting in what is known as "sticky" attention (Bryson et al., 2004; Landry & Bryson, 2004; Sasson et al, 2008): given that autistic participants in our investigation appeared to learn equally effectively from visual and semantic dimensions of stimuli, our findings help to refute the idea that autistic individuals have circumscribed attention and instead might support other recent experiments indicating that individuals with autism are in fact able to disengage from stimuli as readily as members of a neurotypical population (Fischer et al., 2013). Our proposed model might also cohesively account for autistic individuals' attentional and learning deficiencies (Lai et al., 2014). That is, while children with autism likely do not prefer to attend to a single stimulus dimension throughout development, being unable to narrow the breadth of their attention and focus preferentially on some aspects of stimuli and not others, could have serious implications for learning to interact with the environment. Attending to multiple stimulus dimensions can be an ineffective approach to interacting with the environment, given the possibility that the intensity of too much input might prohibit learning on individual stimulus dimensions. Integration of multidimensional stimuli is more practical if an individual already has experience learning from one dimension to begin with.

The conjecture from our study is likewise consistent with the previously posited "Intense World Syndrome" hypothesis, which states that the basis of autism might be associated with a hyperactivity in neural networks located throughout the brain (Markram, Rinaldi, & Markram, 2007). We suggest here that the increased excitation of some neural circuits could be attributed—at least in part—to the down-regulation of inhibitory activity caused by a desensitization of select α_2-adrenergic receptors. Thus, autistic individuals' inability to tolerate a sensory or cognitive overload (Granovetter, 2013a) could possibly be a consequence of an

incapacity to ultimately focus the breadth of attention on any one feature of that individual's environment while ignoring all others.

Our model could also help to explain the social deficits often observed in autistic individuals (Lai et al., 2014), while simultaneously demonstrating that social impairment in autistic individuals is not necessarily a consequence of innate dysfunction of neural circuits specific to social cognitive processes. In our experimental task, autistic participants demonstrated no significant differences in learning about social cues versus learning about nonsocial cues (Figure 3.5). It is unlikely that this is due to a floor effect given that performance on social blocks was lower on one dimension and higher on another, attesting to the dynamic range of performance on our task even around the low levels of learning exhibited by the autistic group. These results suggest that autistic individuals do not necessarily have a specific aversion to social stimuli as has been previously argued (Doherty-Sneddon, Whittle, & Riby, 2013), but rather that they might have a generalized inability to focus their attention on social cues in situations in which it is necessary to narrow the breadth of attention to encompass only social-related features of the environment. Therefore, it is conceivable that an infant who will go on to develop autism might not be capable of attending to and learning specifically from social cues of parents and others with the same proficiency as neurotypical individuals. For example, they might attend to both the emotional expression in a mother's eyes, as well as the eyes' color, but being unable to ever focus on either the semantic or visual features of the eyes at any given time might induce a significant cognitive load that hinders autistic infants' ability to effectively learn social cues. Moreover, attentional and social deficits are perhaps only two of the several autistic features that can be explained using our model, given the LC's extensive range of projections throughout the brain. Implications that autistic individuals undergo abnormal cerebellar development (Wang,

Kloth, & Badura, 2014), for example, might be a downstream consequence of LC modulation of the cerebellum (Figure 4.3).

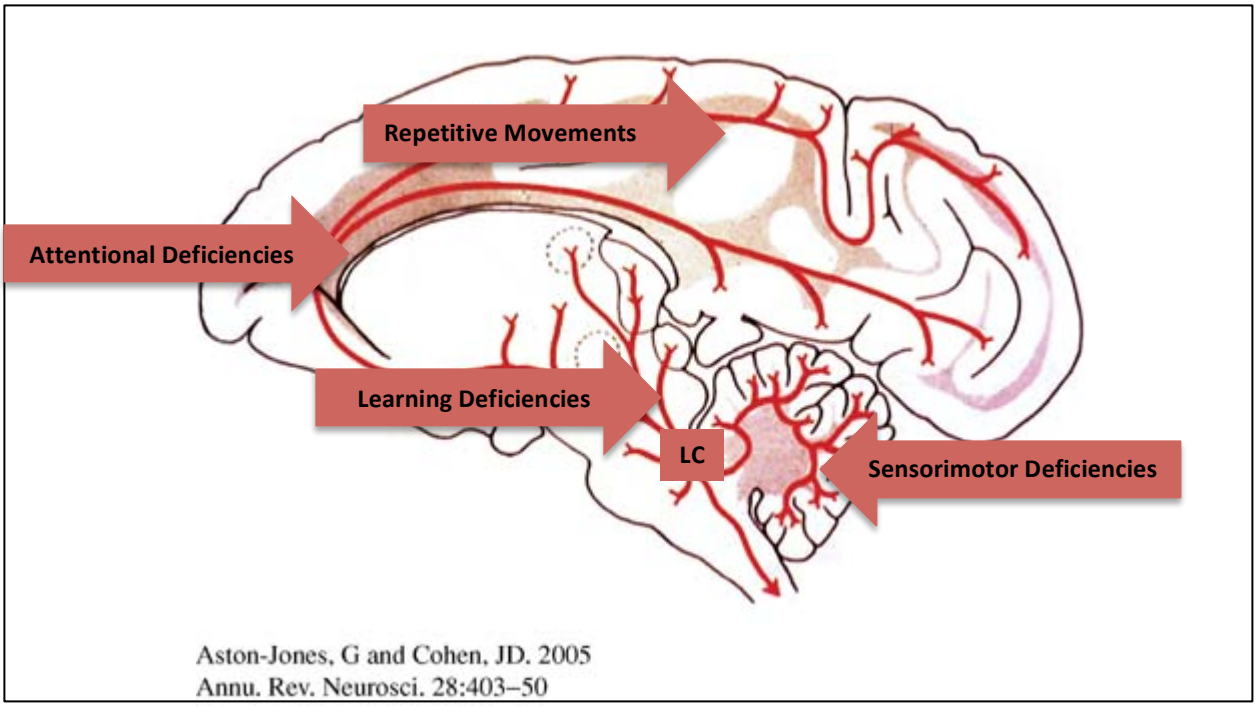


Figure 4.3. An illustration demonstrating how LC's range of targets might be able to explain an array of autistic features, due to abnormal development or regulation of regions receiving LC input. Figure adapted from Aston-Jones & Cohen (2005), also based on Bears et al. (2007), Butler & Hodos (1997), Lai et al. (2014), and Wang et al. (2014).

4.5. Cautions on Interpretation

To substantiate our present findings and the interpretation we suggested above, it is important to replicate this investigation with larger sample sizes in order to increase statistical power. For instance, we were able to demonstrate a significant difference in pupillary responses between autistic participants (all but one of whom exhibited behaviors consistent with the low gain state) and the control participant (of the 6 with pupillometry data that could be analyzed) who exhibited behaviors consistent with the high gain state, but our analysis would have benefitted from data collected from more control participants exhibiting behaviors consistent with the low gain state. At the same time, leaving out the data of the 1 control with the highest

gain (as determined from pupillary responses), we observed a significant difference between autistic participants' and control participants' pupillary responses. That is, the measured pupillary responses were an indicator that overall, autistic participants had higher gain than control participants, but it is necessary to run more participants, so that the controls in our sample exhibit a broader variability in physiological and behavioral features of gain, as would be expected in a general neurotypical population. Likewise, we might anticipate that the correlation between pupillary responses and the covariance between visual performance versus semantic performance might be statistically significant (at the very least for control participants) with larger sample sizes, in light of the findings from Eldar et al. (2013a).

It is also problematic that individuals in each group might interpret the behavioral task differently. That is, the comparison of behavioral performance metrics between the two groups might be inherently limited by the possibility of each population understanding the task differently, as opposed to performing it differently based on a single, correct interpretation. We will not discount our results due to such a possibility, as we attempted to optimally standardize the presentation of the instructions to the two groups (Chapter 2), but the issue of comparing performance on difficult and cognitively demanding tasks between neurotypical individuals and individuals with a mental handicap (whether that might be the result of neurological or psychiatric dysfunction, or even age) is a challenge that cannot be ignored.

Alternatively, autistic individuals might be demonstrating low performance and low pupillary responses given that these individuals are prone to anxiety (Lai et al., 2014), and that negative performance can induce autonomic arousal (Clewett, Schoeke, & Mather, 2014), which is associated with high baseline pupil diameter and consequently, low pupillary responses. We also acknowledge that the heterogeneity of individuals with autism (Lai et al., 2014) might have

an effect on our results, as some participants might have a cognitive challenge with a biological basis that differs from other participants.

4.6. Implications and Future Directions

Some material in this section was adapted from Granovetter (2014).

Current pharmacological treatment regimens available for autistic individuals include antipsychotics to control relatively extreme behaviors, selective serotonin reuptake inhibitors to reduce repetitive behaviors, and stimulants to enhance attention (Lai et al., 2014). However, these drugs have poor receptor selectivity and are not targeted interventions designed with the intention of treating ASD (Granovetter, 2013a; Granovetter, 2013b). While our model suggests a possible neurobiological contribution to autistic attention-based learning features, designing a treatment intervention targeting NE or its receptor would be imperfect in its capability to improve attentional and learning difficulties given that the drug would need to limit adrenergic receptor desensitization, a challenging drug discovery problem. NE reuptake inhibitors, which regulate NE concentrations at the synapse, indeed are used to treat a variety of attentional and psychiatric conditions that can be comorbid with autism (Meyer & Quenzer, 2013). Nevertheless, in light of our model, this intervention could be ineffective due to low availability of NE receptors. Even a NE reuptake inhibitor that is a partial adrenergic receptor antagonist would create problems given the variety of adrenergic receptors that NE can ultimately bind to: some of which can be readily desensitized and others which cannot. Moreover, it is even conceivable that noradrenergic neurons become desensitized to input as a consequence of adrenergic receptor degradation or a down-regulation in receptor production (Figure 4.4; Heck & Bylund, 1997), and thus it is unclear if typical surface expression concentrations of adrenergic receptors could be rescued at the synapse. That being said, chronic administration of

desipramine, a NE reuptake inhibitor, restores social and cognitive deficiencies in the autism mouse model, *Engrailed-2* -/- (Brielmaer et al., 2014), suggesting that reducing NE at the synapse might still be a possible target strategy for developing autism treatments.

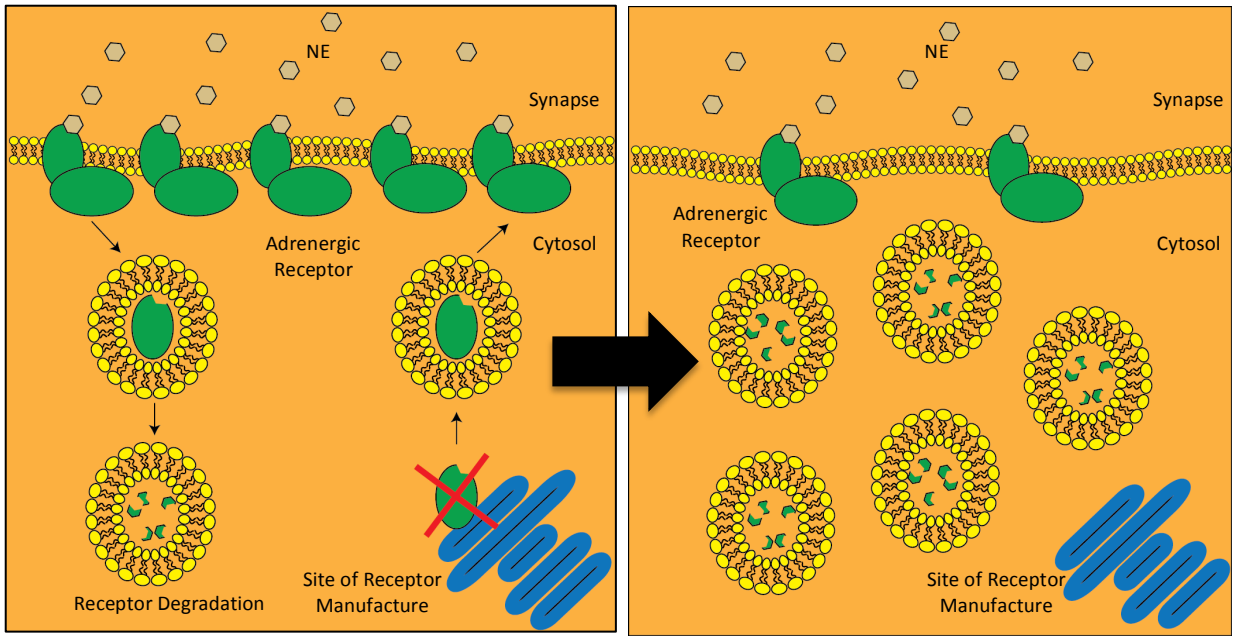


Figure 4.4. The left panel consists of illustrations of the two previously proposed mechanisms by which adrenergic neurons can become desensitized, first delineated in Heck & Bylund (1997). The right panel demonstrates the likely residual effects at the synapse of desensitized adrenergic neurons in the long-term. We suggest that either mechanism might limit changes in gain in autistic individuals who might have up-regulated LC-NE systems.

The effectiveness of pharmacological treatment notwithstanding, current behavioral interventions have similar, if not superior, efficacy compared with pharmacological treatment strategies (Granovetter, 2013b), and such practices could be improved in light of our findings. In particular, interventions could be adapted in order to increase attention to select environmental cues for toddlers with either elevated pupil diameters (thus signifying a risk of autism) or toddlers of siblings of an autistic individual (given the strong genetic risk factors for autism; Ozonoff et al., 2011). For instance, when teaching an individual how to read—not merely to translate the visual input on the page to verbal output, but actually to comprehend the semantic

context of the words—special education professionals could devise ways to limit all other sources of sensory input that might interfere with processing the semantic meaning of words on a page. Such disruptive variables might range from the texture of the page to the lighting in the room, all of which could be treated as neural input that each has a similar effect on neural output as the semantic comprehension of a text's words. As another example, children at high risk for autism might consider methods of increasing attention to facial expressions over other competing sensory input, e.g., by providing such infants with monochromatic glasses during critical periods for social development, in order to limit learning on the visual dimension when learning on the semantic dimension is most crucial. Moreover, perhaps such infants could also be consistently prompted to attend to social stimuli in their environment, such as conspecifics' eye gazes during the critical period for social development identified by Elsabbagh et al. (2013). Either method, along with other possible approaches, might help to ensure that the social circuits in the brain develop appropriately.

Just as importantly, this study, as well as future research on attention-based learning in autistic individuals, might not only help to shed light on the neural basis of autism (thereby accelerating basic neuroscience research efforts utilizing animal models), but such studies could also improve diagnostic criteria and thus allow for earlier identification of the disorder in the clinic. While observing children's attentional processes using saccade movements has already been employed in practice to diagnose children with autism, diagnoses are still being made too late for children on the high-functioning end of the spectrum (Lai et al., 2014). Therefore, since the adrenergic receptors controlling pupillary response to LC activation are not necessarily desensitized, abnormal baseline pupillary responses and deficiencies at integrating multidimensional stimuli could potentially be utilized as likely early signs of autism.

Further research, however, still needs to clarify the causes underlying an individual's capacity to modulate gain. Understanding why a neurotypical individual can transition from a state of high gain to low gain, or vice versa, would help to guide investigations questioning whether and if autistic individuals are indeed constitutively in a single gain state. Assuming that replications of our work validate our current conclusions, another next appropriate step might be to further probe the effects of constitutive LC activity in animal model systems. One might consider observing the effects of LC stimulation in mice over different periods of time, in order to mimic our proposed model for autism in humans, among other potential ways that the LC-NE system could be modulating autistic behaviors. Researchers have already utilized optogenetics to begin to investigate the effects of LC activation on neural circuitry and behavior, in fact demonstrating that increased frequency of LC stimulation results in behaviors reminiscent of human neuropsychiatric conditions in mice (Carter et al., 2010). Future experiments should consider using this technology to stimulate constitutive tonic LC firing in mice (at a rate that could have the least detriment to overall health) over different time periods. Immunohistochemical and in situ hybridization assays could in fact ascertain what effect chronic LC activation might have on NE concentrations at the synaptic terminal and synaptic cleft, as well as postsynaptic adrenergic receptor surface expression and rate of synthesis (Figure 4.4). The findings from such studies, in conjunction with our results and those found from future replications of our work, might indeed offer insight into a cohesive model to explain the neural basis of autism.

Conclusion

Autistic individuals are known to have attention-based learning deficiencies and exhibit elevated baseline pupil diameters. Increased baseline pupil diameter is a characteristic posited to be associated with increased neural gain, consequently influencing attention-based learning. On the basis of this evidence, we conducted an investigation to test for differences in physiological and behavioral responses to an attention-based learning task, in autistic and neurotypical individuals. Our findings revealed that while autistic participants exhibited significantly lower pupillary responses compared with those control participants demonstrating pupillary responses most consistent with the low gain state, autistic participants' learning performances were nonetheless generally consistent with a low gain state. We propose that in light of autistic participants' pupillary responses, autistic individuals likely exhibit chronic concentrations of NE, which might ultimately desensitize adrenergic receptors that modulate attention-based learning, thereby significantly reducing neural gain in autistic participants. While our work requires further validation in a greater number of participants, we believe that our proposal lends support to the claim that tonic LC firing and chronic elevated NE release in autistic individuals modulates select neural circuits in such a way as to hinder attentional focus to and sensory integration of multiple stimulus features in one's environment.

Appendix A

Questionnaire

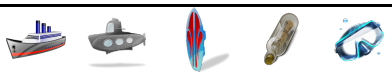
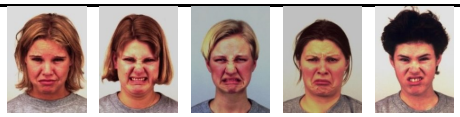
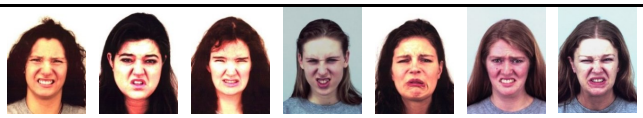
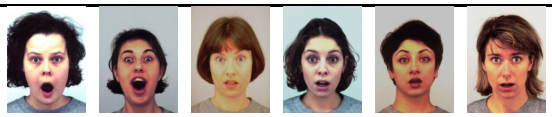
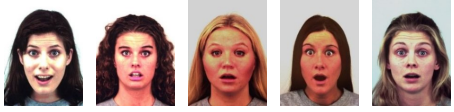
Question	Answer Choices
I would rather be considered	(a) realistic. (b) innovative.
If I were a teacher, I would rather teach a course	(a) that deals with facts and real life situations. (b) that deals with ideas and theories.
I find it easier	(a) to learn facts. (b) to learn concepts.
In reading nonfiction, I prefer	(a) something that teaches me new facts or tells me how to do something. (b) something that gives me new ideas to think about.
I prefer the idea of	(a) certainty. (b) theory.
I am more likely to be considered	(a) careful about the details of my work. (b) creative about how to do my work.
When I am reading for enjoyment, I like writers to	(a) clearly say what they mean. (b) say things in creative, interesting ways.
When I have to perform a task, I prefer to	(a) master one way of doing it. (b) come up with new ways of doing it.

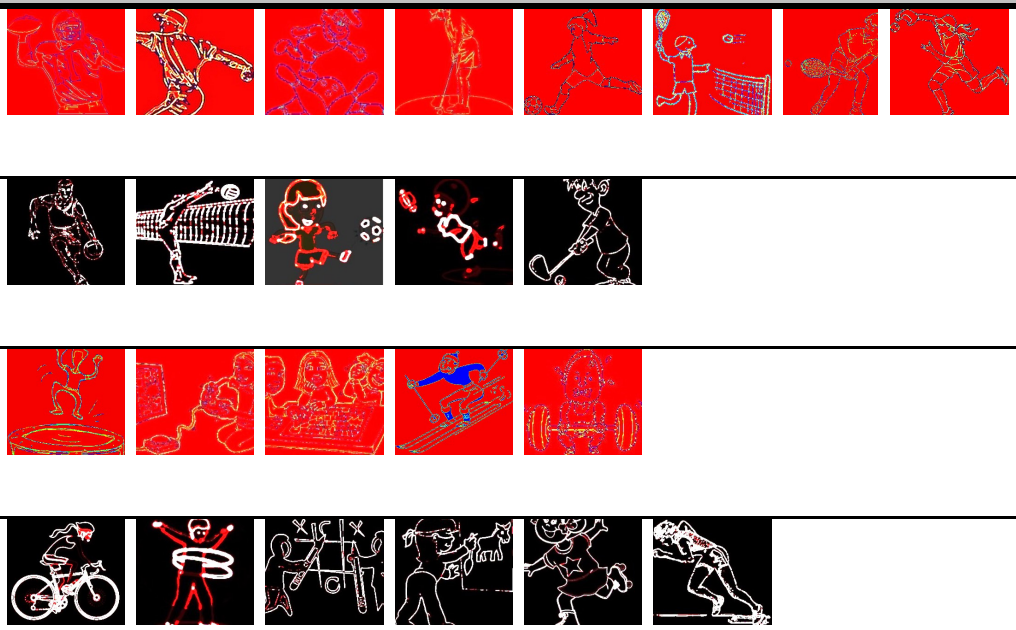
Question	Answer Choices
I consider it higher praise to call someone	(a) sensible. (b) imaginative.
I prefer courses that emphasize	(a) concrete material (facts, data). (b) abstract material (concepts, theories).
When I am doing long calculations,	(a) I tend to repeat all my steps and check my work carefully. (b) I find checking my work tiresome and have to force myself to do it.

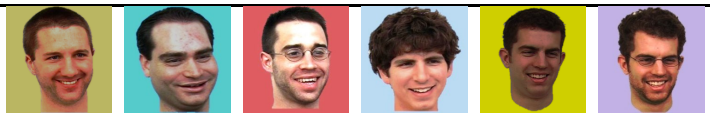
Questions selected from the ILS questionnaire. Adapted from Felder & Spurlin (2005).

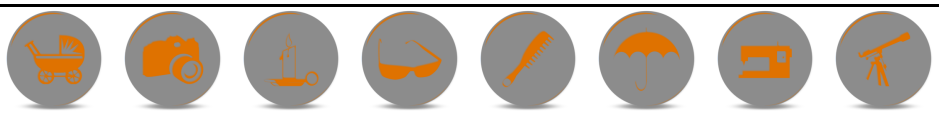
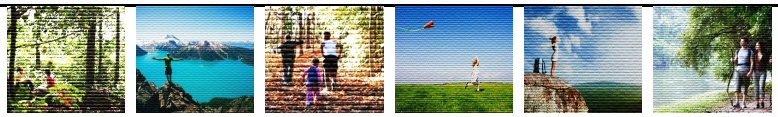
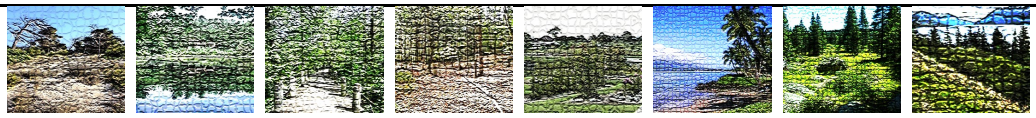
Appendix B

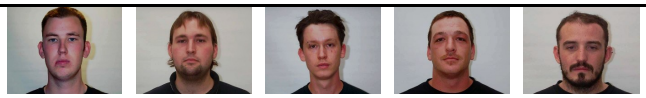
Stimuli

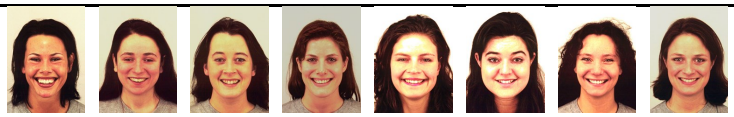
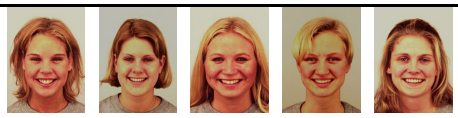
Block Number	Groups of Stimuli with Similar Dimensional Features
1	
	
	
	
2	
	
	
	

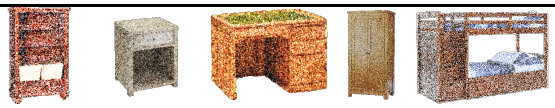
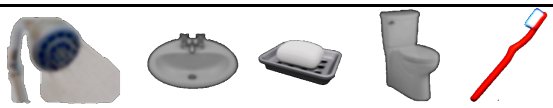
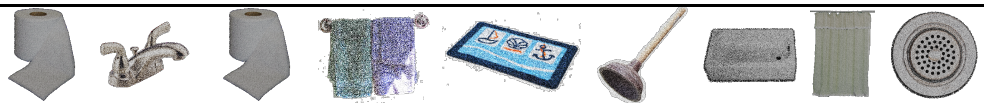
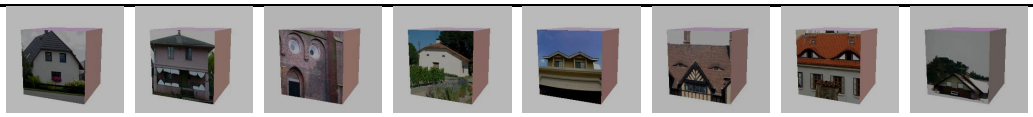
Block Number	Groups of Stimuli with Similar Dimensional Features
3	
4	

Block Number	Groups of Stimuli with Similar Dimensional Features
5	Ape Bear Cow Lion Mule Ox
	Crab Frog Owl Rat Worm
	Buffalo Dolphin Elephant Giraffe Rhinoceros
	Beaver Butterfly Cockroach Dragonfly Oyster Rabbit Scorpion Hedgehog
6	
	
	
	

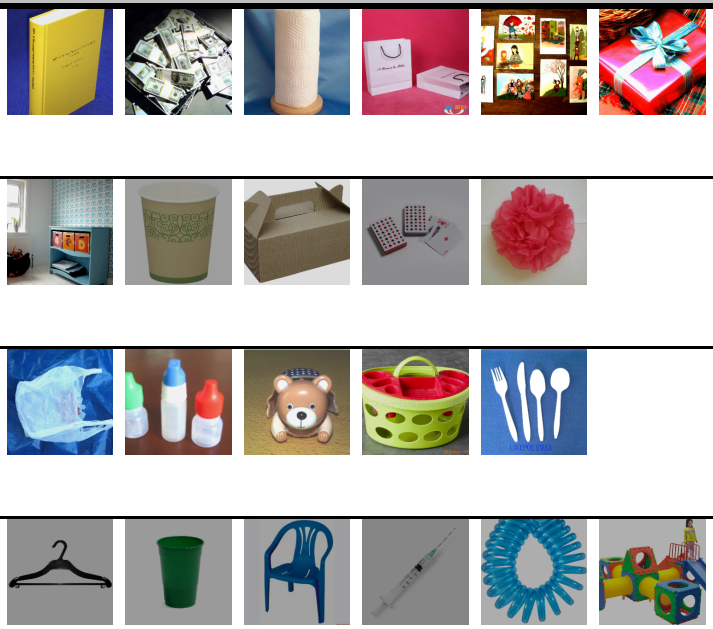
Block Number	Groups of Stimuli with Similar Dimensional Features
7	   
8	   

Block Number	Groups of Stimuli with Similar Dimensional Features
9	   
10	Cheerful Merry Joyful Smiling Grinning Good Sunny Delighted Friendly Happy Glad Unhappy Sorry Mad Miserable Angry Gloomy Upset Sad Cheerless Furious Annoyed Frowning Crying

Block Number	Groups of Stimuli with Similar Dimensional Features
11	
	
	
	
12	
	
	
	

Block Number	Groups of Stimuli with Similar Dimensional Features
13	
	
	
	
14	
	
	
	

Block Number	Groups of Stimuli with Similar Dimensional Features
15	Apricot Blueberry Cherry Kiwi Lime Mandarin Pear Plum
	Apple Banana Grape Orange Peach
	Bean Cauliflower Cabbage Lettuce Pea
	Asparagus Broccoli Carrot Celery Onion Spinach
16	
	
	
	

Block Number	Groups of Stimuli with Similar Dimensional Features
17	
18	

Stimuli. Within each block of stimuli above, items are arranged such that each row displays stimuli with a select visual feature and a select semantic feature. Stimuli from blocks 1, 5, 7, 11, 15, and 17 were used in Eldar et al. (2013a). Stimuli from blocks 2 and 10 were acquired from the Karolinska Directed Emotional Faces (Lundqvist, Flykt, & Öhman, 1998), stimuli from block 9 were acquired from the Center for Vital Longevity Face Database (Minear & Park, 2004), and stimuli from block 6 were acquired from the Face Place (Righi, Peissig, & Tarr, 2012).

Appendix C

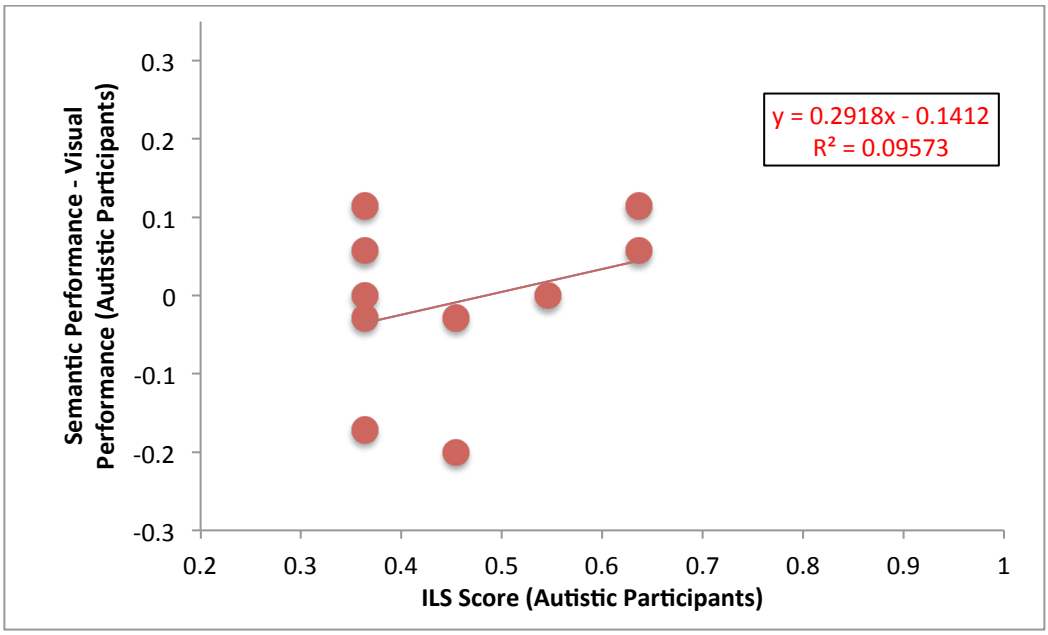
Excluded Participants

Excluded Autistic Participant	Visual Performance (mean ± SEM)	Semantic Performance (mean ± SEM)
1	35.56% ± 6.98%	37.78% ± 3.69%
2	51.43% ± 8.10%	40.00% ± 4.71%

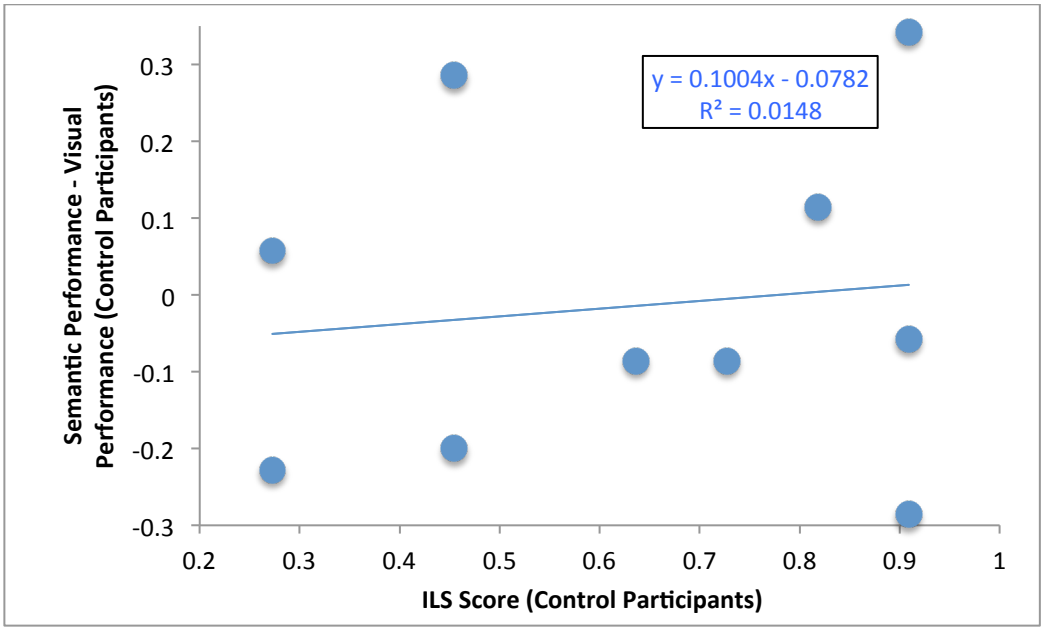
Individual learning performances for participants' whose data was discarded in the final analysis. No control participant data were discarded.

Appendix D

Additional Non-Significant Matched Performance Analyses



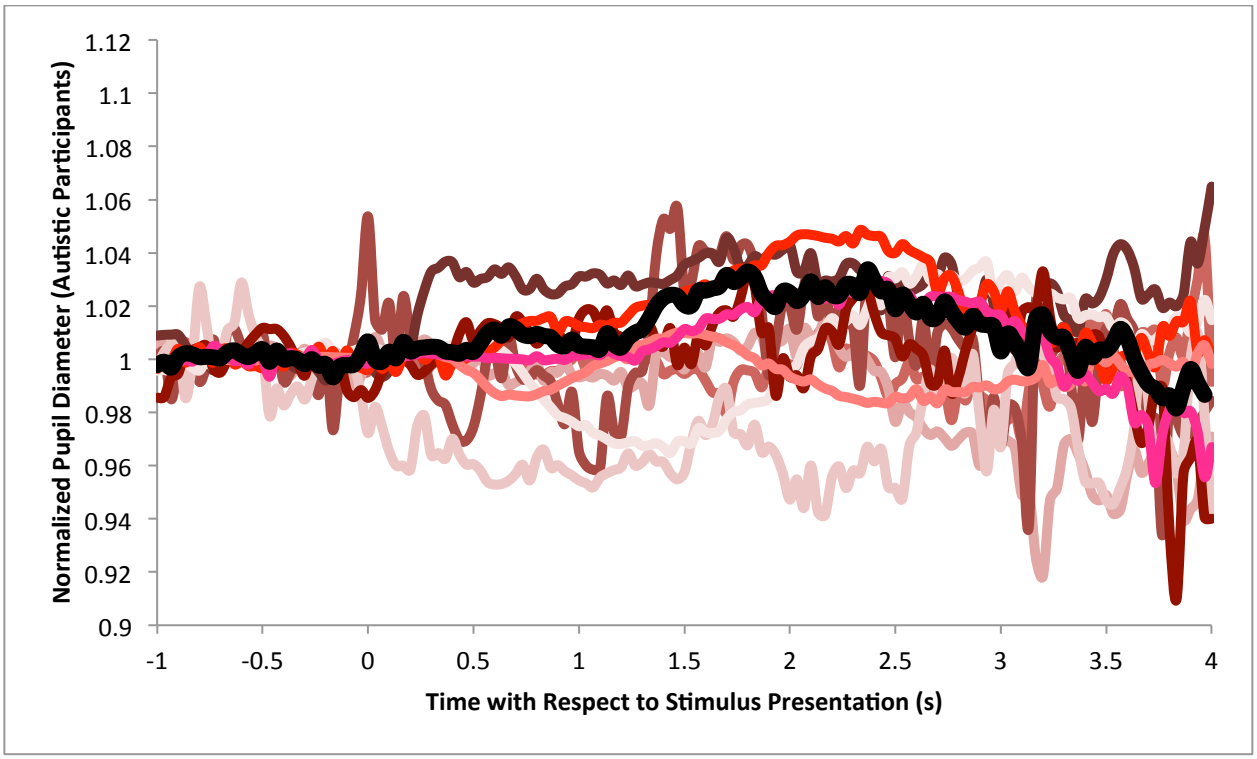
Association between ILS score and the difference between semantic performance and visual performance, across autistic participants, for blocks best matched on performance.



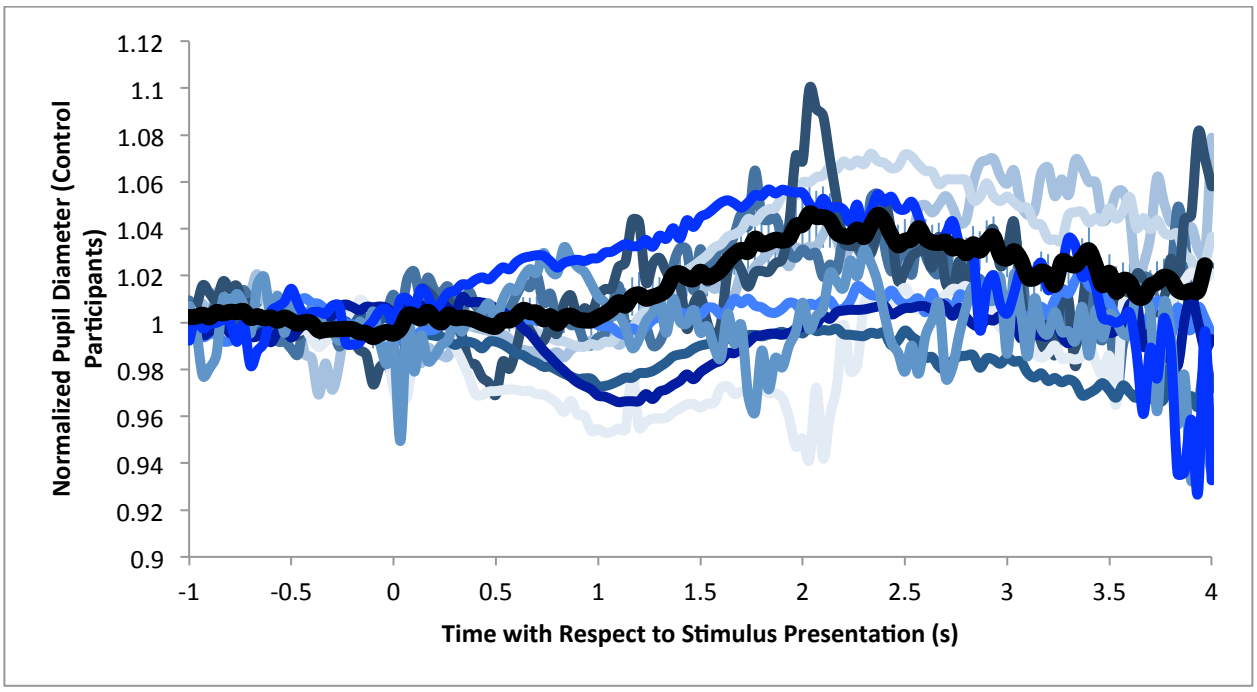
Association between ILS score and the difference in semantic performance and visual performance, across control participants, for blocks best matched on performance.

Appendix E

Individual Mean Pupillary Responses



Mean pupillary response across trials for each autistic participant. The black line shows the mean pupillary response averaged across all autistic participants.



Mean pupillary response across trials for each control participant. The black line shows the mean pupillary response averaged across all control participants.

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Please use this form to indicate the relationship between previous work and your senior thesis and to indicate whether your thesis involved collaboration with others.

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My senior thesis was a natural and thorough extension of the ideas originally posited in my junior independent work. Material that was used in my junior independent work appears throughout much of Chapters 1 and 2, as well as Section 4.5 (as cited at the start of each of these chapters and section). This is largely because the hypothesis that I proposed to test in my junior independent work did not change significantly in the senior thesis. Therefore, much of my background literature review and methods, as well as part of the study's implications and future directions, are the same in both my junior independent work and senior thesis. While my junior independent work was mostly a research proposal, my senior thesis reflects the work that I conducted throughout my senior year, during which all experimentation, as well as data analysis and interpretation took place.

My senior thesis is a research investigation that I conducted as a member of the Niv lab, in collaboration with my advisor, Yael Niv, and former Princeton University graduate student (and current University College of London post-doctoral fellow) Eran Eldar. Given that my study design was adapted from a previous project in the lab, the code for my experiment was adapted from an in-house code, with the assistance of Dr. Eldar. That being said, the experimental design used in this study had a range of differences from the previous investigation conducted in the lab, and I initiated all study design modifications. Some scripts used to perform the analyses were written independently by myself, while some were written in collaboration with Dr. Eldar and Dr. Niv. I ran the experiment, collected all of the data myself, and analyzed and interpreted the data myself, with some consultation from Dr. Eldar and Dr. Niv.

Approval Form for Undergraduate Research Involving Experimental Animals

All research involving experimental animals at Princeton University must receive the prior approval from the Institutional Animal Care and Use Committee (IACUC). The IACUC bases decision about approval on the NRC Guide for the Care and Use of Laboratory Animals. All students conducting research involving animals as part of their junior independent work or senior thesis must receive approval from the IACUC prior to beginning their research. Students should consult first with their advisers about whether the procedures they intend to use are already covered by previously approved submission to the IACUC. The IACUC meets only once a month and it is common for new submissions to require revision before receiving approval so students are strongly encouraged to attend to IACUC issues early in their planning.

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