The Reward Endophenotype in Autism: Implications for Understanding Affective, Cognitive, and Behavioral Function Across the Spectrum

By

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Dissertation
Submitted to the Faculty of the
Graduate School of Vanderbilt University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY
in

Neuroscience
August 11, 2017
Nashville, Tennessee

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DEDICATION

To my mom, who answers every phone call, talks me down off every ledge, celebrates even the smallest successes, and has been my most faithful editor since I learned how to write

and

To my people, who continually remind me where my identity is to be found

ACKNOWLEDGEMENTS

The product of this dissertation is most certainly the reflection of the work of a community, of which I would like to thank some specific individuals. First, thank you to the members of the Bodfish lab – Kathryn Slaboch, Allison Whitten, Robin Shafer, Sahana Nagabhushan, Paige Goodie, Emily Morrow, and Jessica Goldstein – for helping me to be a better scientist by asking difficult questions, listening to hours of practice presentations, and reminding me to take breaks and laugh a little. I am proud to call each of you my colleague. Second, thank you to the members of my dissertation committee – Dr. Carissa Cascio, Dean Mark Wallace, and Dr. Beth Malow. Each of you wear many hats, and the fact that you chose to say "yes" to mentoring me through my dissertation is not something that I take for granted. I am honored that you have chosen to invest so much into the development of my academic career. I would also like to express my gratitude for the administrative team in the Vanderbilt Brain Institute office, specifically Roz Johnson and Beth Sims. You made the small details of my life so much easier, and knowing I didn't have to think about those things helped me to focus fully on my science.

Dr. Bodfish, thank you for being the mentor that I never knew I needed. The process of writing and presenting my dissertation has given me an opportunity to see just how much I have grown over the last 5 years. Much of that growth is a direct reflection of your commitment to mentorship. Thank you for believing in my ability even when I was too intimidated to see it. Thank you for pushing me outside of the limits of my comfort. Thank you for choosing to see me as a scientist and a colleague, rather than as a research project. Your mentorship has been the

single most salient aspect of my time at Vanderbilt, and I hope that I can continue to contribute to the autism research field in a way that honors your investment.

Thank you to my Nashville community and my Trinity Church family. You have walked with me through the highs and lows of graduate school. You have fed me, encouraged me, cried with me, asked questions about my science with genuine interest, delivered emergency ice cream and flowers, proof-read papers, and allowed me to do countless loads of laundry in your homes. You are my family, and because of you, Nashville will always feel like home.

Finally, I would like to thank my parents, Stan and Vickie Unruh, for working tirelessly and selflessly to ensure I was financially and emotionally supported throughout my years of school. I will always be grateful for the way you have encouraged me to write my own story, but have never allowed me to settle for less than my best. And thank you to my little brother, Ryan, for putting up with me even during my worst years and never failing to make me laugh.

This work would not have been possible without the generous financial support of the National Institute of Mental Health (NIMH R01 MH073402), National Institute of Child Health and Human Development (NICHD R01 HD 082127), and the Autism Speaks Dennis Weatherstone Predoctoral Fellowship (9557).

OVERVIEW

Two behavioral domains form the diagnostic criteria for autism spectrum disorder (ASD). This neurodevelopmental disorder is marked by deficits in social and communicative behaviors and the presence of restricted and repetitive behaviors and interests, which tend to be primarily nonsocial in nature. Despite their equal contribution to the autism phenotype, the bulk of research to date has focused on understanding and addressing socio-communicative behaviors, while the the pathogenesis of repetitive behaviors remains largely understudied. Further, little work has been done to understand how these co-occurring behaviors may interact with one another to influence the presentation of ASD across development. This dissertation will focus one mechanism that may play a role in contributing to the combined expression of both socio-communicative and repetitive behavior domains in ASD. The core phenotype of ASD is a pattern of *deficient* social behavior and *enhanced* nonsocial behavior. One model for such a pattern is that mechanisms of reward processing play a dynamic role and contributes to both aspects of this phenotype.

The purpose of this dissertation was to develop novel measurement techniques and collect empirical data to elucidate the role for a reward endophenotype in autism. I begin by critically evaluating the existing literature of reward processing in autism, focusing on the social motivation theory of autism and identification of critical gaps in this model that can be used to guide additional research in this area. Following this, a series of studies is presented to test a proposed dynamic model of motivation in ASD that can account for differences in both social and nonsocial motivation. These studies utilize behavioral phenotyping, eye-tracking, and

electroencephalography (EEG) to provide tests of this dynamic motivation model and also to examine whether distinct aspects of the autism phenotype may be related to a common underlying mechanism of reward processing. These studies also examine whether these bio-behavioral measures of reward processing are sensitive to detecting ASD-related differences (a) during early childhood, (b) across levels of cognitive impairment characteristic that are of the autism spectrum, and (c) in comparison to depression, another reward-related neuropsychiatric disorder. Finally, I discuss the overall contribution of this line of research, in the context of extant literature, and outline implications for how these findings may influence the field of autism clinically and in terms of future research.

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CHAPTER 1

INTRODUCTION

The social motivation theory of autism

The social motivation theory of autism (Dawson, 1991; Dawson & Lewy, 1989) has become one of the leading conceptual models for understanding autism spectrum disorders (ASD) and for guiding research in this area. Prior to the introduction of this motivational account of ASD, theoretical accounts of autism focused primarily on deficits in cognitive processes that were presumed to underlie the expression of phenotypic aspects of autism – for example Weak Central Coherence (Frith, 1989), Theory of Mind (Simon Baron-Cohen, 1997), and Executive Dysfunction (Gillberg & Coleman, 2000; Ozonoff, Pennington, & Rogers, 1991). In contrast to these earlier models, the social motivation theory highlights the fact that in individuals with ASD, performance deficits on cognitive tasks consistent with these frameworks are often exaggerated or only present for social stimuli. For example, many children with ASD are particularly impaired when prompted to respond to their own name. In experiments using auditory orienting tasks, Dawson and colleagues found that children with ASD exhibited specific deficits in orienting to social stimuli, compared to typically developing (TD) and developmentally delayed peers, but not to nonsocial stimuli (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Since this seminal study, many others have found autism-related deficits in social orienting and attention (e.g., Čeponienė et al., 2003; Lepistö et al., 2005; Pierce et al., 2016; Pierce, Conant, Hazin, Stoner, & Desmond, 2011; Sasson & Touchstone, 2014; Zwaigenbaum et al., 2005). Based on these types of findings, the social motivation theory proposes that cognitive performance in ASD is influenced by

deficiencies in motivation to attend to and process social information, and that this social motivation deficit drives differences in social development and social behavior that are defining features of ASD.

The social motivation theory is derived from the hypothesis that reward is disrupted in ASD (Dawson, 1991). The mechanistic basis for this model critically sets it apart from the three aforementioned cognition-based models of ASD. Importantly, this model posits that dysfunctional reward may contribute to deficits observed across many different processes described in pre-existing theories of autism due to the fundamental role of reward in guiding behavior. We live in a world that contains a multitude of stimuli to attend and respond to, and thus it is evolutionarily beneficial to possess neural processes that direct our behavior toward adaptive choices. This is particularly significant for social processes, as the neural mechanisms that underlie social behavior interact with reward circuitry to promote increased engagement in these experiences (Insel, 2003). Healthy function of reward circuitry is malleable, allowing our previous experiences to shape our future behavior, such that positive experiences promote increased engagement in certain behavioral choices, while negative experiences deter behavior. The information to which we orient and attend forms the basis for our experiences, and these experiences shape both behavioral and neural development. However, disruption of reward processes can lead to aberrant seeking and experience of reward, which may promote altered patterns of behavior and perpetuate further alterations in neural processing of reward. The social motivation hypothesis suggests that in ASD, divergence in reward processing may occur very early in life. It is well known that socio-communicative development is critically dependent upon early social experiences, most notably parent-child interactions. It can be seen how a child who consistently attends to social information will amass significantly different early life experiences from a peer who fails to orient to

social information and therefore may be set on a trajectory for atypical social-communication that is a core feature of ASD (Dawson, 1991).

A critical evaluation of the social motivation theory

Although the social motivation theory of autism has been important for guiding new research in autism, there are critical gaps in this model in relation to what we know about the *nonsocial* aspects of ASD and also in relation to what we know about how motivation and reward-related information is processed in the brain in order to guide reward-related behavior and development. We reason that a critical appraisal of these gaps can lead to an expanded motivational model of ASD that may help to guide novel research aimed to increase our understanding of this condition.

Instances of intact reward

The social motivation theory is built upon the supposition that reward is dysfunctional in ASD. Since its proposal, there have been many demonstrations in the literature that reward dysfunction does exist (e.g., Delmonte et al., 2012; Kohls et al., 2012; Schmitz et al., 2008; Zeeland et al., 2010). However, there are also demonstrations of intact reward in individuals with ASD that are difficult to account for based on the social motivation framework. For example, both monetary and social rewards have been associated with improved task performance in ASD, at a level that is either comparable to or increased from TD controls, for reaction time (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2011), response inhibition (Pankert, Pankert, Herpertz-Dahlmann, Konrad, & Kohls, 2014), and instrumental reward learning (Lin, Rangel, & Adolphs, 2012). Individuals with ASD are also willing to work for preferred items, suggesting intact motivational mechanisms. This has been demonstrated experimentally, as individuals with ASD are willing to expend increased effort to view face and car images (Ewing, Pellicano, &

Rhodes, 2013), object images (Watson et al., 2015), and earn money (Damiano, Aloi, Treadway, Bodfish, & Dichter, 2012). Intact reward is further demonstrated through numerous exemplars of intervention practices that effectively utilize reinforcement as a strategy for shaping behavior (e.g., Carr, Nicolson, & Higbee, 2000; Eldevik et al., 2009; Karsten & Carr, 2009).

Components of reward may be differentially affected

One potential limitation of the social motivation theory is that it applies only a unitary model of reward. Research outside of ASD has shown that reward can be dissociated into two components, which are the consequence of distinct neuroanatomy / circuitry and unique neurochemical systems (e.g., Berridge & Robinson, 2003; Knutson, Fong, Adams, Varner, & Hommer, 2001; Smith, Berridge, & Aldridge, 2011). The implication of applying this dual-component model of reward to ASD is that, in this state, performance may be differentially related to enhancements or deficits in either or both of these components. Consummatory reward is defined as the affective experience of pleasure during the consumption of a stimulus (Berridge & Robinson, 1998). This "liking" response involves neurotransmission of opioid / gamma-Aminobutyric acid (GABA) systems and endocannabinoids and is associated with increased activity in the ventromedial prefrontal cortex (Knutson et al., 2001). Anticipatory reward is defined as motivated or approach behavior elicited by either the sensory properties of a hedonic stimulus or the cues associated with that stimulus (Berridge & Robinson, 1998). Reward "wanting" critically involves dopaminergic activity (Berridge, Venier, & Robinson, 1989; Smith et al., 2011; Yun, Wakabayashi, Fields, & Nicola, 2004) and activity in the ventral striatum (Knutson et al., 2001) and amygdala regions of the human brain (Hommer et al., 2003). The social motivation theory fails to account for these mechanistically different aspects of reward processing and reward-related

behavior. Thus the potential roles that these distinct mechanisms may play in influencing development and behavior in the context of ASD may be lost within a more general social motivation framework.

Social deficits are nuanced and may be secondary to other behavior

The social motivation theory proposes that orienting and attending to social information is deficient in ASD. Visual attention to social information has been tested extensively in ASD using eye-tracking. Several studies have demonstrated significant differences in facial fixation patterns, with individuals with ASD looking less to eye regions and more to mouth regions than TD controls (Corden, Chilvers, & Skuse, 2008; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002; Riby & Hancock, 2008a, 2008b; Spezio, Adolphs, Hurley, & Piven, 2006). However, look time to faces (e.g., Bar-Haim, Shulman, Lamy, & Reuveni, 2006; Fletcher-Watson, Leekam, Findlay, & Stanton, 2008; Van Der Geest, Kemner, Verbaten, & Van Engeland, 2002) or social figures (S. Fletcher-Watson, Leekam, Benson, Frank, & Findlay, 2009; Van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2002) does not always differ between groups. By studying social information in isolation, the focus is immediately placed on where individuals with ASD are *not* looking, rather than asking the question of what they are looking to *instead*. In a seminal social eye-tracking study, Klin and colleagues demonstrated that while individuals with ASD spend less time looking to "socially relevant" regions of the face, they look two times *more* to object information than TD controls. This pattern of increased nonsocial (object) attention paired with decreased social attention has been observed across a variety of eye-tracking paradigms (Elison, Sasson, Turner-Brown, Dichter, & Bodfish, 2012; Fletcher-Watson et al., 2009; Pierce et al., 2015, 2011; Riby & Hancock, 2008b; Sasson & Touchstone, 2014; Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008), suggesting that while social attention may be diminished, enhancement in nonsocial attention may warrant equal consideration.

Accounting for ASD-specific nonsocial behavior

The primary focus of the social motivation theory is to explain the pattern of deficient social-communication behaviors that are characteristic of ASD. However, this focus leaves out an equally characteristic feature of ASD: increased restricted and repetitive behavior and interests. These behaviors tend to be nonsocial in nature. A prominent exemplar of the nonsocial nature of these behaviors is the presence of circumscribed interests, which are commonly reported in individuals with ASD (Anthony et al., 2013; South, Ozonoff, & McMahon, 2005; Turner-Brown, Lam, Holtzclaw, Dichter, & Bodfish, 2011). The interests of children with ASD markedly differ from their TD peers. Although interests in ASD are often referred to as "restricted" or "circumscribed," studies have shown that it is not necessarily the number of interests that differ between children with ASD and TD (Anthony et al., 2013; Turner-Brown et al., 2011; Unruh et al., 2016). Rather, the phenomenology of these interests differs. Qualitatively, the interests of individuals with ASD are far more likely to fall into the category of 'folk physics' which encompasses knowledge of the mechanical and nonsocial aspects of the world, rather than 'folk psychology' which is concerned with the social aspects of the world (Baron-Cohen & Wheelwright, 1999). Engagement with these interests is also far more likely to be done in solitude, rather than in a social context (South et al., 2005; Turner-Brown et al., 2011). Parents of individuals with ASD report that interest engagement in ASD, compared to interest engagement in the typical population, is increased in its frequency / duration, and in the amount of resistance met when interrupted, accommodation that must be provided by families, and interference with the quality of family life (South et al., 2005). Therefore, these behaviors may significantly restrict the developmental experiences of children with ASD (Pierce & Courchesne, 2001), and if so, understanding the role of motivational

processes in the development and instantiation of these nonsocial aspects of the ASD phenotype is critical.

An alternative model: The dynamic motivation theory of autism

The current model of social motivation in autism has moved the field forward by providing a novel and generative motivational framework for understanding autism-related cognition and behavior. However, this model does not account for the co-occurrence of both social and nonsocial aspects of the ASD phenotype, and it is not consistent with contemporary models of how reward-related information is processed in the brain to guide reward-related behavior and development. Therefore, we propose an expanded model that incorporates both the social and nonsocial features of ASD and puts forth biologically plausible reward-guided mechanisms by which these patterns of behavior may develop. This expanded motivational model of ASD postulates two putative biologically plausible mechanisms that could be operative in the development of the complex and opposing social / nonsocial phenotype that is characteristic of ASD: first, processes related to "motivational toxicity" borrowed from existing research on addictive disorders, and second, plasticity-related processes that can drive experience-dependent canalization of behavioral development.

Motivational toxicity and the development of inflexible patterns of behavior

In reward-related disorders such as addiction, dynamic reward circuitry becomes hijacked by a narrow set of activities and experiences (e.g., substances of abuse, in the case of addiction). In this way, disrupted patterns of motivation can contribute to altered behavioral development that results in narrow and inflexible behavioral repertoires. This phenomenon is known in the addiction literature as "motivational toxicity." Motivational toxicity describes the way in which increased motivation to pursue

pleasurable behaviors (i.e. the activities of addiction), over time, contributes to a decrease in motivation to pursue other types of behavior. Motivational toxicity has been reported in a variety of clinical disorders, including substance abuse (Esch & Stefano, 2004), some types of disordered eating (e.g., Smith & Robbins, 2013), and non-drug forms of addiction such as compulsive internet use (e.g., Young, 1998) or gambling (e.g., Petry, 2006). These disorders present with a specific motivational profile: as the behaviors related to the addiction increase (e.g., drug intake, compulsive eating patterns, internet use) there is a corresponding reduction in the reward value of other forms of activity, such as social relationships, vocational activities, and pursuit of other hobbies.

Neural development is guided by experience

Just as reward has the potential to guide experiences, in turn, these experiences shape brain and behavioral development. The propensity for experiences to direct brain development is illustrated in the context of typical development. For example, just after birth, the infant brain responds similarly to many different languages (Kuhl, Conboy, Padden, Nelson, & Pruitt, 2005). However, by 4 months of age, an infant will respond more strongly to the language spoken in his environment than languages he has not experienced (Friederici, Friedrich, & Christophe, 2007). Analogous effects can be seen in the development of visual preference for a mother's face over a stranger (Pascalis & Kelly, 2009) and in a variety of other sensory and cognitive abilities (Fox, Levitt, & Nelson III, 2010). In these scenarios, brain development has the potential to be guided, such that skills and behaviors are promoted according to individual sets of experiences.

Application of these motivational mechanisms to ASD

Considering the totality of research findings on reward and motivation in ASD, autism can be characterized by a dynamic pattern of motivation that includes both *enhanced* motivation to nonsocial sources of stimulation and *diminished* motivation to social sources of stimulation. *If enhanced nonsocial motivation is present early in life, this specific motivational profile could contribute to both the social and nonsocial behavioral phenotype in ASD through mechanisms of dynamic motivation, including motivational toxicity and experience-dependent development*. It is reasonable to assume, given the behavioral phenotype of ASD, that these individuals accrue more nonsocial experiences and fewer social experiences than their TD peers. Excessive engagement in nonsocial experiences (e.g., repetitive behaviors and interests that are characteristic of ASD) may "crowd out" opportunities for more social experiences. The implication of this altered experiential pattern is two-fold. First, within the framework of motivational toxicity, it can be recognized that social and nonsocial motivation may be related and interactive in the mechanistic sense, rather than disparate or acting in isolation of one another. If a bias toward nonsocial motivation is present early in life, increased engagement in nonsocial behaviors may drive a diminished motivation to engage in social behaviors. Second, these altered motivational patterns would also, then, shape both immediate experience and the way in which cumulative experience grows and shapes brain development. In the context of ASD, a heightened motivation for nonsocial information likely leads to an increase in the number of nonsocial experiences in which a child engages. This pattern of experience may, therefore, "canalize" or restrict experience-dependent brain development to favor the development of nonsocial patterns of behavior or skills at the expense of social patterns of behavior or skills.

Empirical support for the dynamic motivation model

Enhanced nonsocial motivation is present in ASD

Early experiences in ASD differ markedly from those in typical development, even prior to diagnosis. Play behaviors are a primary context in which children can acquire and practice skills that are necessary for appropriate interactions in the social world (Lifter & Bloom, 1989; Parten, 1932; Smilansky, 1968). However, children who go on to be diagnosed with ASD tend to engage in nonsocial interests at the expense of engaging in functional play behaviors, with studies reporting increased object attachment and preoccupation (Mooney, Gray, Tonge, Sweeney, & Taffe, 2009) and increased stereotyped and repetitive object play (Honey, Leekam, Turner, & McConachie, 2007; Morgan, Wetherby, & Barber, 2008) compared to TD peers. The presence of increased nonsocial behavior has been shown to differentiate children who go on to be diagnosed with ASD from developmentally delayed peers as early as 12 months of age (Ozonoff et al., 2008; Werner & Dawson, 2005).

Nonsocial information biases attention

The presence of specific types of nonsocial information can bias attentional patterns in ASD. Individuals with ASD exhibit increased viewing time to specific types of nonsocial images (Sasson, Dichter, & Bodfish, 2012), even at the expense of gaining monetary reward (Watson et al., 2015). Several studies have quantified nonsocial bias using arrays that contain two image types, showing that for individuals with ASD, the presence of specific nonsocial images can restrict engagement with social information (Elison et al., 2012; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011; Sasson & Touchstone, 2014). This bias may also extend to attentional orienting, as individuals with ASD take longer to fixate on social images when they are paired with specific nonsocial images (Sasson & Touchstone, 2014;

Unruh et al., 2016). Importantly, this bias does not appear to be present for nonsocial images previously shown to be of neutral valence to individuals with ASD.

Enhanced activation of reward circuitry to nonsocial information

Evidence from imaging studies supports the notion that specific types of nonsocial information may differentially engage brain reward circuitry in individuals with ASD, relative to social sources of information. Neural regions associated with reward, including the insula and ventromedial prefrontal cortex (vmPFC) have shown increased activity in ASD compared to TD controls when viewing both general nonsocial images (Dichter et al., 2012) and those related to a child's specific nonsocial interest (Cascio et al., 2014). Evidence also suggests that in ASD, reward-related areas of the brain show differential patterns of functional activation when engaging with nonsocial information compared to other information types. Thus far, one study has demonstrated that for nonsocial reward (earning the ability to view an image), there is robust activation of the the nucleus accumbens during reward anticipation in both typical development and ASD, but that increased activity in the vmPCF during reward consumption is restricted to individuals with ASD (Dichter et al., 2012).

Enhanced nonsocial motivation is related to phenotypic characteristics of ASD

Engagement in play behaviors has been shown to be related to the development of further socio-communicative skills (e.g., expressive language abilities) in both TD children and those with ASD (Honey et al., 2007). Similarly, object-focused repetitive behaviors in early ASD have been shown to be related to or predictive of social-communicative skills later in life (Lam, Bodfish, & Piven, 2008; Szatmari et al., 2006; Watt, Wetherby, Barber, & Morgan, 2008). Notably, there is evidence that other repetitive behaviors, like insistence on sameness and compulsions (i.e. those that are not overtly

nonsocial in nature) do not show this same relationship with social development (Szatmari et al., 2006; Watt et al., 2008).

Nonsocial interest is associated with functional impairment in social domains

Clinical reports suggest that nonsocial interests in ASD may also be related to a lack of social interest (Smith et al., 2009) and have been reported to negatively impact an individual's ability to socialize (Mercier, Mottron, & Belleville, 2000). Empirical studies have shown that the degree to which nonsocial interest contributes to functional impairment in an individual can be significantly predicted by sensitivity to motivational aspects of reward (Damiano et al., 2012) and is positively correlated with reward-related neural responses when viewing nonsocial images (Cascio et al., 2014). The magnitude of an individual's nonsocial bias during visual tasks is also associated with increased severity of repetitive behaviors (Sasson et al., 2008) and increased engagement with nonsocial interests (Unruh et al., 2016). Correspondingly, at least one study has demonstrated an inverse relationship between nonsocial bias and psychometric measures of social functioning and social interest (Sasson et al., 2008).

ASD shows neurobiological similarities to other reward-related disorders

The striatum is an anatomical region in the basal ganglia involved in the dynamic modulation of motivated behavior (Graybiel, 2008) and is a primary target of drugs of abuse. Addiction is associated with widespread structural and metabolic changes in striatal circuitry, including increased striatal volume (Chang, Alicata, Ernst, & Volkow, 2007). One of the most robust neuroanatomical findings in the ASD literature is increased volume of the caudate nucleus (Haznedar et al., 2006; Hollander et al., 2005; Langen et al., 2009, 2014; Langen, Durston, Staal, Palmen, & van Engeland, 2007; Rojas et al., 2006; Sears et al., 1999), both when controlling for total brain volume (Haznedar et al., 2006; Hollander

et al., 2005; Langen et al., 2007; Voelbel, Bates, Buckman, Pandina, & Hendren, 2006) and age (Langen et al., 2014; Rojas et al., 2006). Developmentally, the size of the caudate may increase with age in ASD, while decreasing in the trajectory of typical development. In ASD, these volumetric increases are associated with increased expression of repetitive behavior (Langen et al., 2009, 2014).

Dopaminergic mechanisms are associated with changes in motivated behavior

A variety of neurochemicals contribute to the specific motivational profiles seen in reward-related disorders. Drugs of abuse are historically associated with DA, as many cause increases in extracellular DA in mesolimbic / striatal brain regions. A primary aspect of addiction is altered dopamine signaling; cues associated with addictive substances / behaviors cause increases in striatal dopamine independent of drug delivery, and this process is sufficient to promote the increased pursuit of drug / behavioral reward (Volkow et al., 2002, 2006). Upon drug administration, drug abusers show significantly less striatal DA release compared to healthy controls (Volkow et al., 1997), but report increased drug craving. Therefore, addiction illustrates the way in which dopaminergic abnormalities can lead to changes in behavior. Response to drug was among the earliest indication that DA dysfunction may play a role in ASD. Very early pharmacological studies of the DA antagonist haloperidol found that it was effective in reducing "uncooperativity," and hyperactivity (Campbell et al., 1978; Perry et al., 1989), and some aspects of repetitive behavior (stereotypies, abnormal object relationships) and was associated with mild improvements on a reward-learning task (Campbell et al., 1982). Conversely, the use of stimulants, which promote DA release and block uptake and clearance, has been reported to exacerbate symptoms of ASD in some individuals (Anderson & Hoshino, 1997). While no drugs are currently approved to treat core symptoms of ASD, two atypical antipsychotic drugs with prominent dopaminergic activity (Risperidone and Aripiprazole) have been shown to be effective in treating some

symptoms associated with ASD. Treatment groups show significant reductions in problem behaviors (e.g., aggression, irritability, hyperactivity), compared to placebo (McDougle et al., 2005; Nagaraj, Singhi, & Malhi, 2006; Pandina, Bossie, Youssef, Zhu, & Dunbar, 2007; Shea et al., 2004). There is also evidence that these drugs may reduce stereotypy in some patients (Marcus et al., 2009; Owen et al., 2009).

Measurement of peripheral dopaminergic activity in ASD has led to equivocal findings regarding group differences, with some studies reporting no group differences (Minderaa, Anderson, Volkmar, Akkerhuis, & Cohen, 1989; Narayan, Srinath, Anderson, & Meundi, 1993; Ross, Klykylo, & Anderson, 1985; Winsberg, Sverd, Castells, Hurwic, & Perel, 1980) and others finding significant alterations between adults with ASD and TD controls (Alabdali, Al-Ayadhi, & El-Ansary, 2014; Gillberg & Svennerholm, 1987; Gillberg, Svennerholm, & Hamilton-Hellberg, 1983). However, two studies have reported positive correlations between levels of central dopamine and stereotypy in individuals with ASD (Cohen et al., 1979; Cohen, Caparulo, Shaywitz, & Bowers, 1977). Dopaminergic alterations in ASD may also be circuit-specific. Adults with ASD have shown increased levels of presynaptic DA in the striatum and frontal cortex (Nieminen-von Wendt et al., 2004) and increased binding capacity of the dopamine transporter, specifically in the orbitofrontal cortices (Nakamura et al., 2010). Developmental effects may also exist, as increased striatal dopamine binding capacity has been observed in young children with ASD, compared to TD peers, but is decreased in older children with ASD.

The DA transporter (DAT) regulates dopaminergic transmission through high-affinity re-uptake of DA in the synapse. This transporter is notably affected during addiction, where drugs such as cocaine and amphetamine interact with the transporter and alter dopaminergic transmission. There is also evidence

that DAT is affected during behavioral addiction, as recent studies have demonstrated decreased DAT expression in the striatum of individuals with internet addiction disorder (Hou et al., 2012) and pathological gambling (Cilia et al., 2010). Specific polymorphisms of DAT have been associated with increased risk for binge-eating disorder (Davis et al., 2007; Shinohara, Mizushima, Hirano, Shioe, & others, 2004). Preliminary evidence also suggests that genetic differences in DAT expression may modulate the way in which an individual responds to cues associated with addictive behaviors (Franklin et al., 2008).

Mutations in DAT (SLCA3) have been identified in select individuals with ASD. Functional characterization of these mutations has revealed anomalous DA efflux, rather than the typical pattern of transporting DA into the cell (Cartier et al., 2015; Hamilton et al., 2013), as well as atypical transporter trafficking (Bowton et al., 2014), both of which can significantly impact neurotransmission. Alterations in DAT function have been hypothesized to contribute to widespread changes in dopaminergic tone in ASD (Emanuele, 2015). Among the processes regulated by DA are plasticity, dendritic spine morphology, and synaptogenesis, which have been implicated in ASD pathogenesis (Nguyen et al., 2014) and illustrate the widespread neuromodulatory effects that may result from altered dopaminergic tone.

Specific genetic DA receptor variants are also associated with increased risk for reward-related disorders. The D2-receptor (DRD2) is one of the most widely studied receptor variants in addiction (Noble, 2000). The *Taq*1 A allele has been associated with reduced D2 receptor binding and expression in the human striatum (Thompson et al., 1997), and behaviorally, with reduced sensitivity to reward value (Kirsch et al., 2006). Although widely known for its association with risk for alcoholism, this

allele is also associated with the severity of pathological gambling (Comings et al., 1996), risk for obesity (Noble et al., 1994), and reward sensitivity in individuals with binge-eating disorder (Davis et al., 2008). A review of the SFARI gene database has also suggested that select polymorphisms of both D1-like and D2-like receptors are implicated in risk for ASD (Nguyen et al., 2014). The *Taq*1 A allele has been found with increased incidence in individuals with ASD (Comings et al., 1991; Salem et al., 2013). A recent study demonstrated an association between this allele and ASD-related behavioral deficits in infants at high risk for ASD (Gangi, Messinger, Martin, & Cuccaro, 2016). Specific polymorphisms of the DRD2 receptor have also been associated with increased severity of both socio-communicative and repetitive behaviors in individuals with ASD (Hettinger et al., 2012).

GABAergic manipulation contributes to shifts in dynamic motivational patterns

The inhibitory neurotransmitter GABA is involved in reward through its modulatory effect on dopaminergic tone in the striatum and ventral tegmental area (Vlachou & Markou, 2010). GABAergic alterations in ASD are widespread, including both increased neuronal density in cerebellar and hippocampal regions (Blatt et al., 2001; Lawrence, Kemper, Bauman, & Blatt, 2010) and decreased density in the amygdala and fusiform gyrus (van Kooten et al., 2008). Individuals with ASD also show reduced GABA receptor density in several neural regions associated with reward circuitry, including the hippocampus and cingulate cortex (Oblak, Gibbs, & Blatt, 2009; Oblak, Gibbs, & Blatt, 2010), frontal cortex (Mori et al., 2012) and, notably, the amygdala and nucleus accumbens (Mendez et al., 2013). Higher GABA plasma levels (Dhossche et al., 2002; El-Ansary & Al-Ayadhi, 2014; El-Ansary, Bacha, & Al-Ayahdi, 2011) and altered expression of glutamic acid decarboxylase, the rate-limiting step of GABA (Yip, Soghomonian, & Blatt, 2007, 2008), have also been reported in ASD. Microduplications in the chromosome 15q11-13 have been observed in some individuals with ASD (Buxbaum et al., 2002;

Cook et al., 1998; McCauley et al., 2004; Menold et al., 2001; Sebat et al., 2007; Shao et al., 2003); duplications in this region have been associated with reduced GABA receptor expression. Abnormal expression of genes in the 15q11-13 locus have also been associated with ASD even in the absence of a mutation, resulting in a reduction of $GABA_A$ receptor density (Hogart, Nagarajan, Patzel, Yasui, & Lasalle, 2007).

GABAergic manipulations are sufficient to alter the rewarding properties of substances of abuse. Both rodent and human studies have demonstrated the effectiveness of GABA agonists in decreasing drug administration (Kumar, Sharma, Kumar, & Deshmukh, 2013; McElroy et al., 2003; Tyacke, Lingford-Hughes, Reed, & Nutt, 2010) and ameliorating patterns of binge-eating behavior (Berner, Bocarsly, Hoebel, & Avena, 2009; Guardia, Rolland, Karila, & Cottencin, 2011; McElroy et al., 2003). Arbaclofen is a selective $GABA_B$ receptor agonist that has previously been used to reduce the motivational properties of drugs of abuse (Kim & Lawrence, 2014). A recent study in ASD found administration of Arbaclofen to be associated with improvements in social function and communication (Erickson et al., 2014).

Implications of the dynamic motivation model

Convergence with contemporary domain-based approaches to clinical neuroscience research

The Research Domain Criteria (RDoC) approach was proposed by the National Institutes of Mental Health to revise the way mental disorders are conceptualized and studied. Rather than a symptom-specific approach, RDoC proposes five general domains of functioning (e.g., positive valence systems, systems for social processes). Within these domains, specific constructs, or functional dimensions of behavior, have been identified. This provides a framework within which to study common functional

impairments among separate diagnoses, thus compiling information in an extensive matrix of genes, molecules, cells, circuits, physiology, behavior, self-report questionnaires, and behavioral paradigms that are associated with each specific construct.

The behaviors described here align with the functional dimensions of the Positive Valence Systems domain (e.g., reward valuation, responsiveness to reward attainment, habit). In this way, research within ASD may focus on *mechanism* (altered motivational mechanisms), rather than symptom (repetitive behaviors and impaired socio-communicative behaviors). This approach provides a framework to identify other disorders that may share common mechanisms, including addiction, schizophrenia, obsessive compulsive disorder, and depression. For example, to date, the bulk of reward-related research in ASD has not considered the component model of reward, although preliminary evidence suggests that components may be differentially affected. The study of addiction exemplifies the significance of focusing on the components of reward. Seminal studies by Volkow and colleagues in the area of cocaine addiction revealed that prolonged drug abuse is associated with diminished responses in neural regions associated with reward consumption, and, therefore, it is not an enhanced hedonic response to drug that perpetuates addiction. Rather, cocaine "hijacks" the dopaminergic neurons that underlie the attribution of incentive salience / reward wanting (Volkow et al., 1995). Therefore, drug abusers show enhanced neural responses to cues associated with drug taking, which are associated with behavioral reports of drug craving (Volkow et al., 1997; Volkow et al., 2008). Further, this enhanced response to drug cues is paired with a decreased response to other reward-related cues, even those previously known to be highly pleasurable (e.g., explicit images; Dunning et al., 2011), which illustrates the significance of motivational toxicity in the pathology of addiction. This differential impact of reward components is critical in developing effective therapeutic approaches. Such studies have informed treatments that target

the processes involved in anticipatory reward (e.g., dopaminergic and GABAergic mechanisms) as well as behaviorally altering environments that may be rampant with cues that trigger craving responses.

The case of addiction helps highlight the potential importance of studying ASD in relation to other disorders, rather than relying upon typical development as the sole group of comparison. This approach has begun to gain popularity in some aspects of ASD research, including comparing social avoidance and anxiety behaviors between individuals with diagnoses of ASD and those with diagnoses of social anxiety disorder. Another comparison that is becoming increasingly common is that of ASD to ADHD, as there are known reward deficits in ADHD regarding anticipatory reward (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2011b; van Hulst et al., 2016). However, future studies examining these differences for a variety of reward types (e.g., social and nonsocial) may provide more insight into the specificity or generality of reward abnormalities in ASD. It is noteworthy that up to 60% of individuals with ASD have co-morbid diagnoses or co-occurring symptomology of ADHD; however, by using a domain-based approach rather than a symptom or diagnostic-based approach, this overlap has the potential to be informative, rather than confounding.

Aiding early identification of ASD

Studies have shown that many children who receive early, intensive intervention make significant gains in communication and functional skills (e.g., Howard, Sparkman, Cohen, Green, & Stanislaw, 2005; Lovaas, 1987; Sallows, Graupner, & MacLean Jr, 2005), and that some children make such significant developmental gains that they are no longer considered to have a disability (Dawson, 2008). Further, early intervention may be critical in targeting trajectories of neural development (Dawson, 2008; Dawson et al., 2012). At present, the earliest age for reliable diagnosis of ASD is 24 months (Lord et al.,

2006), although the CDC estimates the average age of diagnosis at 4 years (Christensen, 2016). Diagnosis of ASD is currently based on behavioral measures, which rely heavily upon the lack of development of social behaviors that may not be reliably detected as deficient until the second year of life. However, recent research suggests that measurement of ASD-specific repetitive behaviors may be a relatively more effective approach to identification of ASD prior to 12 months of age. Notably, nonsocial attention during the first year of life may be particularly relevant in differentiating infants who go on to be diagnosed with ASD from those with typical development or other developmental delays. Both atypical object exploration and increased object (nonsocial) interest have been shown to differentiate infants who are later diagnosed with ASD from peers (Maestro et al., 2002, 2005; Osterling, Dawson, & Munson, 2002; Ozonoff et al., 2008; Pierce et al., 2015, 2011). Therefore, development of tools that capitalize upon measurement of nonsocial motivation in ASD, rather than those that rely upon missed developmental milestones, may prove valuable in efforts toward early identification.

Novel direction for intervention research

There are currently very few evidence-based therapies approved to treat the core symptoms of ASD. Of these, most are targeted at improving language / socio-communicative skills, in other words, targeting behaviors (e.g., Dawson et al., 2010). The dynamic motivation model, on the other hand, provides a framework for addressing the *mechanisms* that may underlie the core behaviors that are characteristic of ASD. Further understanding of reward mechanisms, and nonsocial reward, in particular, may guide the development of new treatment approaches.

One direction for this mechanistic approach is to seek therapies that increase social motivation. However, the dynamic motivation model suggests that leveraging of nonsocial motivation may also be a direction to consider for improving functional outcomes for individuals with ASD. Historically, the presence of nonsocial behavior was targeted as a behavior to extinguish (e.g., Lovaas, 1987; Nefdt, Koegel, Singer, & Gerber, 2010; Smith et al., 2010). In contrast, based on a dynamic motivational perspective, approaches that scaffold the development of new skills upon a foundation of nonsocial behaviors that the child prefers to engage in, may also hold promise.

There is a small literature examining the effectiveness of nonsocial behavior-focused interventions. These studies have shown that integrating aspects of a child's specific nonsocial interests into a task has a positive influence on the outcome of the intervention. This effect is seen for both academic (Adams, 1999; Charlop-Christy & Haymes, 1996; Mancil & Pearl, 2008) and play / social skills (Baker, 2000; Baker, Koegel, & Koegel, 1998; Boyd, Conroy, Mancil, Nakao, & Alter, 2006; Boyd, McDonough, & Bodfish, 2011; Kryzak, Bauer, Jones, & Sturmey, 2013; Porter, 2012; Vismara & Lyons, 2007). Using the child's own interests as a point of entry for shaping behavior has been particularly effective in at least two types of caregiver-mediated interventions. Joint Attention, Symbolic Play, Engagement and Regulation (JASPER; Kasari, Gulsrud, Wong, Kwon, & Locke, 2010) builds social and communicative opportunities (e.g., joint attention) from the child's self-directed behavior. This approach has been shown to increase and maintain joint attention and diversify play behaviors in toddlers with ASD, including children who were considered to have "minimal verbal ability" (Kasari et al., 2010; Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015; Vismara & Lyons, 2007). A second approach to nonsocial intervention is Family-Implemented Treatment for Behavioral Inflexibility (FITBI; Boyd, McDonough, Rupp, Khan, & Bodfish, 2010); one aspect of this intervention involves shaping nonsocial

behaviors that have the potential to be functionally appropriate. This intervention has been shown to be effective in building a more flexible and socially appropriate behavioral repertoire in at least some children with ASD.

Conclusion

Converging evidence from studies of genetics, neuroanatomy, and neural connectivity implicate alterations in reward circuitry in the pathogenesis of ASD. However, the functional consequences of these alterations are not well understood. An established model of ASD, the social motivation theory, addresses the potential contribution of atypical reward processing to social symptomology. Alternatively, the dynamic motivation model is able to account more comprehensively for the full social and nonsocial features of the ASD phenotype by extending the social motivation theory of autism in several key ways. First, this extended model provides a framework for understanding the joint occurrence of decreased social and increased nonsocial behaviors. Further, the current model provides a set of biologically plausible mechanisms that could be explored in the context of ASD to help gain a greater mechanistic understanding of reward-related behavior and development in ASD.

A novel implication of this model is that social motivation and related social attention / orientation mechanisms may be intact or at least more plastic than previously assumed in ASD, but may be overcome by competing nonsocial motivations and experiences. As such, specific types of nonsocial information may interfere with social attention, and consequently, the development of social behaviors. Another novel implication of this model is that it may help account for the established increased comorbidity of other disorders in ASD, like depression and ADHD, as these disorders have established links to deficits in reward-related mechanisms. Going forward, studies designed to test this model must deviate from many established ASD paradigms by testing responses to both social and disorder-specific nonsocial information, as well as their interaction. In addition, empirical testing of this dynamic model of motivation in ASD should include developmental studies that can determine if enhanced

nonsocial motivation occurs early in ASD and subsequently disrupts social motivation and the development of social skills. Finally, this model has implications for the search for biomarkers that are critical to the success of translational research in ASD. If true, then the dynamic motivation model of ASD indicates the need for reliable and valid neural markers (e.g., EEG, eye-tracking) of both social and nonsocial reward processing that could be studied across the full spectrum of autistic impairment and across the stages of ASD development.

REFERENCES

Adams, L. W. (1999). *Incorporating narrow interests into the school tasks of children with autism*. University of North Carolina at Chapel Hill.

Alabdali, A., Al-Ayadhi, L., & El-Ansary, A. (2014). Association of social and cognitive impairment and biomarkers in autism spectrum disorders. J Neuroinflammation, 11(4).

Anderson, G. M., & Hoshino, Y. (1997). Neurochemical studies of autism. *Handbook of Autism and Pervasive Developmental Disorders, Volume 1, Third Edition*, 453–472.

Anthony, L. G., Kenworthy, L., Yerys, B. E., Jankowski, K. F., James, J. D., Harms, M. B., … Wallace, G. L. (2013). Interests in high-functioning autism are more intense, interfering, and idiosyncratic than those in neurotypical development. *Development and Psychopathology*, *25*(03), 643–652.

Baker, M. J. (2000). Incorporating the Thematic Ritualistic Behaviors of Children with Autism into Games Increasing Social Play Interactions with Siblings. *Journal of Positive Behavior Interventions*, *2*(2), 66–84. https://doi.org/10.1177/109830070000200201

Baker, M. J., Koegel, R. L., & Koegel, L. K. (1998). Increasing the Social Behavior of Young Children with Autism Using Their Obsessive Behaviors. *Research and Practice for Persons with Severe Disabilities*, *23*(4), 300–308. https://doi.org/10.2511/rpsd.23.4.300

Bar-Haim, Y., Shulman, C., Lamy, D., & Reuveni, A. (2006). Attention to eyes and mouth in high-functioning children with autism. *Journal of Autism and Developmental Disorders*, *36*(1), 131–137.

Baron-Cohen, S. (1997). Mindblindness: An essay on autism and theory of mind. MIT press.

Baron-Cohen, S., & Wheelwright, S. (1999). "Obsessions" in children with autism or Asperger syndrome. Content analysis in terms of core domains of cognition. *The British Journal of Psychiatry*, *175*(5), 484–490. https://doi.org/10.1192/bjp.175.5.484

Berner, L. A., Bocarsly, M. E., Hoebel, B. G., & Avena, N. M. (2009). Baclofen suppresses binge eating of pure fat but not a sugar-rich or sweet-fat diet. *Behavioural Pharmacology*, *20*(7), 631.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*(3), 309–369.

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences*, *26*(9), 507–513.

Berridge, K. C., Venier, I. L., & Robinson, T. E. (1989). Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function. *Behavioral Neuroscience*, *103*(1), 36.

Blatt, G. J., Fitzgerald, C. M., Guptill, J. T., Booker, A. B., Kemper, T. L., & Bauman, M. L. (2001). Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study. *Journal of Autism and Developmental Disorders*, *31*(6), 537–543.

Bowton, E., Saunders, C., Reddy, I. A., Campbell, N. G., Hamilton, P. J., Henry, L. K., … others. (2014). SLC6A3 coding variant Ala559Val found in two autism probands alters dopamine transporter function and trafficking. *Translational Psychiatry*, *4*(10), e464.

Boyd, B. A., Conroy, M. A., Mancil, G. R., Nakao, T., & Alter, P. J. (2006). Effects of Circumscribed Interests on the Social Behaviors of Children with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *37*(8), 1550–1561. https://doi.org/10.1007/s10803-006-0286-8

Boyd, B. A., McDonough, S. G., & Bodfish, J. W. (2011). Evidence-Based Behavioral Interventions for Repetitive Behaviors in Autism. *Journal of Autism and Developmental Disorders*, *42*(6), 1236–1248. https://doi.org/10.1007/s10803-011-1284-z

Boyd, B. A., McDonough, S. G., Rupp, B., Khan, F., & Bodfish, J. W. (2010). Effects of a Family-Implemented Treatment on the Repetitive Behaviors of Children with Autism. *Journal of Autism and Developmental Disorders*, *41*(10), 1330–1341. https://doi.org/10.1007/s10803-010-1156-y

Buxbaum, J. D., Silverman, J. M., Smith, C. J., Greenberg, D. A., Kilifarski, M., Reichert, J., … Vitale, R. (2002). Association between a GABRB3 polymorphism and autism. *Molecular Psychiatry*, *7*(3), 311–316. https://doi.org/10.1038/sj.mp.4001011

Campbell, M., Anderson, L. T., Meier, M., Cohen, I. L., Small, A. M., Samit, C., & Sachar, E. J. (1978). A comparison of haloperidol and behavior therapy and their interaction in autistic children. *Journal of the American Academy of Child Psychiatry*, *17*(4), 640–655.

Campbell, M., Anderson, L. T., Small, A. M., Perry, R., Green, W. H., & Caplan, R. (1982). The effects of haloperidol on learning and behavior in autistic children. *Journal of Autism and Developmental Disorders*, *12*(2), 167–175.

Carr, J. E., Nicolson, A. C., & Higbee, T. S. (2000). Evaluation of a brief multiple-stimulus preference assessment in a naturalistic context. *Journal of Applied Behavior Analysis*, *33*(3), 353–357.

Cartier, E., Hamilton, P. J., Belovich, A. N., Shekar, A., Campbell, N. G., Saunders, C., … others. (2015). Rare autism-associated variants implicate syntaxin 1 (STX1 R26Q) phosphorylation and the dopamine transporter (hDAT R51W) in dopamine neurotransmission and behaviors. *EBioMedicine*, *2*(2), 135–146.

Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P., … Cao, A. (2014). Affective neural response to restricted interests in autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*(2), 162–171.

Čeponienė, R., Lepistö, T., Shestakova, A., Vanhala, R., Alku, P., Näätänen, R., & Yaguchi, K. (2003). Speech–sound-selective auditory impairment in children with autism: they can perceive but do not attend. *Proceedings of the National Academy of Sciences*, *100*(9), 5567–5572.

Chang, L., Alicata, D., Ernst, T., & Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction*, *102*(s1), 16–32.

Charlop-Christy, M. H., & Haymes, L. K. (1996). Using obsessions as reinforcers with and without mild reductive procedures to decrease inappropriate behaviors of children with autism. *Journal of Autism and Developmental Disorders*, *26*(5), 527–546.

Christensen, D. L. (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR. Surveillance Summaries*, *65*. https://doi.org/10.15585/mmwr.ss6503a1

Cohen, D. J., Caparulo, B. K., Shaywitz, B. A., & Bowers, M. B. (1977). Dopamine and serotonin metabolism in neuropsychiatrically disturbed children: CSF homovanillic acid and 5-hydroxyindoleacetic acid. *Archives of General Psychiatry*, *34*(5), 545–550.

Cohen, D. J., Shaywitz, B. A., Young, J. G., Carbonari, C. M., Nathanson, J. A., Lieberman, D., … Maas, J. W. (1979). Central biogenic amine metabolism in children with the syndrome of chronic multiple tics of Gilles de la Tourette: norepinephrine, serotonin, and dopamine. *Journal of the American Academy of Child Psychiatry*, *18*(2), 320–341.

Comings, D. E., Comings, B. G., Muhleman, D., Dietz, G., Shahbahrami, B., Tast, D., … Kovacs, B. W. (1991). The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA*, *266*(13), 1793–1800.

Comings, D. E., Rosenthal, R. J., Lesieur, H. R., Rugle, L. J., Muhleman, D., Chiu, C., … Gade, R. (1996). A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics and Genomics*, *6*(3), 223–234.

Cook, E. H., Courchesne, R. Y., Cox, N. J., Lord, C., Gonen, D., Guter, S. J., … Courchesne, E. (1998). Linkage-disequilibrium mapping of autistic disorder, with 15q11-13 markers. *American Journal of Human Genetics*, *62*(5), 1077–1083. https://doi.org/10.1086/301832

Corden, B., Chilvers, R., & Skuse, D. (2008). Emotional modulation of perception in Asperger's syndrome. *Journal of Autism and Developmental Disorders*, *38*(6), 1072–1080.

Damiano, C. R., Aloi, J., Treadway, M., Bodfish, J. W., & Dichter, G. S. (2012). Adults with autism spectrum disorders exhibit decreased sensitivity to reward parameters when making effort-based decisions. *Journal of Neurodevelopmental Disorders*, *4*, 13. https://doi.org/10.1186/1866-1955-4-13

Davis, C., Levitan, R. D., Kaplan, A. S., Carter, J., Reid, C., Curtis, C., … Kennedy, J. L. (2007). Dopamine Transporter Gene (DAT1) Associated with Appetite Suppression to Methylphenidate in a Case–Control Study of Binge Eating Disorder. *Neuropsychopharmacology*, *32*(10), 2199–2206. https://doi.org/10.1038/sj.npp.1301348

Davis, C., Levitan, R. D., Kaplan, A. S., Carter, J., Reid, C., Curtis, C., … Kennedy, J. L. (2008). Reward sensitivity and the D2 dopamine receptor gene: A case-control study of binge eating disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(3), 620–628.

Dawson, G. (1991). VIII A Psychobiological Perspective on the Early Socio-emotional Development of Children with Autism. *Models and Integrations*, *3*, 207.

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, *20*(03), 775–803.

Dawson, G., Jones, E. J., Merkle, K., Venema, K., Lowy, R., Faja, S., … others. (2012). Early behavioral intervention is associated with normalized brain activity in young children with autism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(11), 1150–1159.

Dawson, G., & Lewy, A. (1989). Arousal, attention, and the socioemotional impairments of individuals with autism. Retrieved from http://psycnet.apa.org.proxy.library.vanderbilt.edu/psycinfo/1989-97258-003

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders*, *28*(6), 479–485.

Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., … Varley, J. (2010). Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*, *125*(1), e17–e23.

Delmonte, S., Balsters, J. H., McGrath, J., Fitzgerald, J., Brennan, S., Fagan, A. J., & Gallagher, L. (2012). Social and monetary reward processing in autism spectrum disorders. *Molecular Autism*, *3*(1), 1.

Demurie, E., Roeyers, H., Baeyens, D., & Sonuga-Barke, E. (2011). Common alterations in sensitivity to type but not amount of reward in ADHD and autism spectrum disorders. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *52*(11), 1164–1173. https://doi.org/10.1111/j.1469-7610.2010.02374.x

Dhossche, D., Applegate, H., Abraham, A., Maertens, P., Bland, L., Bencsath, A., & Martinez, J. (2002). Elevated plasma gamma-aminobutyric acid (GABA) levels in autistic youngsters: stimulus for a GABA hypothesis of autism. *Medical Science Monitor*, *8*(8), PR1–PR6.

Dichter, G. S., Felder, J. N., Green, S. R., Rittenberg, A. M., Sasson, N. J., & Bodfish, J. W. (2012). Reward circuitry function in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *7*(2), 160–172.

Dunning, J. P., Parvaz, M. A., Hajcak, G., Maloney, T., Alia-Klein, N., Woicik, P. A., … Goldstein, R. Z. (2011). Motivated attention to cocaine and emotional cues in abstinent and current cocaine users–an ERP study. *European Journal of Neuroscience*, *33*(9), 1716–1723.

El-Ansary, A., & Al-Ayadhi, L. (2014). GABAergic/glutamatergic imbalance relative to excessive neuroinflammation in autism spectrum disorders. *Journal of Neuroinflammation*, *11*(1), 1.

El-Ansary, A. K., Bacha, A. B., & Al-Ayahdi, L. Y. (2011). Relationship between chronic lead toxicity and plasma neurotransmitters in autistic patients from Saudi Arabia. *Clinical Biochemistry*, *44*(13), 1116–1120.

Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2009). Meta-analysis of early intensive behavioral intervention for children with autism. *Journal of Clinical Child & Adolescent Psychology*, *38*(3), 439–450.

Elison, J. T., Sasson, N. J., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2012). Age trends in visual exploration of social and nonsocial information in children with autism. *Research in Autism Spectrum Disorders*, *6*(2), 842–851.

Emanuele, E. (2015). Does reverse transport of dopamine play a role in autism? *EBioMedicine*, *2*(2), 98–99. https://doi.org/10.1016/j.ebiom.2015.01.012

Erickson, C. A., Veenstra-Vanderweele, J. M., Melmed, R. D., McCracken, J. T., Ginsberg, L. D., Sikich, L., … others. (2014). STX209 (arbaclofen) for autism spectrum disorders: an 8-week open-label study. *Journal of Autism and Developmental Disorders*, *44*(4), 958–964.

Esch, T., & Stefano, G. B. (2004). The neurobiology of pleasure, reward processes, addiction and their health implications. *Neuroendocrinology Letters*, *25*(4), 235–251.

Ewing, L., Pellicano, E., & Rhodes, G. (2013). Using Effort to Measure Reward Value of Faces in Children with Autism. *PLOS ONE*, *8*(11), e79493. https://doi.org/10.1371/journal.pone.0079493

Fletcher-Watson, S., Leekam, S. R., Benson, V., Frank, M. C., & Findlay, J. M. (2009). Eye-movements reveal attention to social information in autism spectrum disorder. *Neuropsychologia*, *47*(1), 248–257.

Fletcher-Watson, S., Leekam, S. R., Findlay, J. M., & Stanton, E. C. (2008). Brief report: Young adults with autism spectrum disorder show normal attention to eye-gaze information—Evidence from a new change blindness paradigm. *Journal of Autism and Developmental Disorders*, *38*(9), 1785–1790.

Fox, S. E., Levitt, P., & Nelson III, C. A. (2010). How the Timing and Quality of Early Experiences Influence the Development of Brain Architecture. *Child Development*, *81*(1), 28–40. https://doi.org/10.1111/j.1467-8624.2009.01380.x

Franklin, T. R., Lohoff, F. W., Wang, Z., Sciortino, N., Harper, D., Li, Y., … Childress, A. R. (2008). DAT Genotype Modulates Brain and Behavioral Responses Elicited by Cigarette Cues. *Neuropsychopharmacology*, *34*(3), 717–728. https://doi.org/10.1038/npp.2008.124

Friederici, A. D., Friedrich, M., & Christophe, A. (2007). Brain responses in 4-month-old infants are already language specific. *Current Biology: CB*, *17*(14), 1208–1211. https://doi.org/10.1016/j.cub.2007.06.011

Frith, U. (1989). Autism: Explaining the enigma. Retrieved from http://onlinelibrary.wiley.com.proxy.library.vanderbilt.edu/doi/10.1348/026151003322277801/full

Gangi, D. N., Messinger, D. S., Martin, E. R., & Cuccaro, M. L. (2016). Dopaminergic variants in siblings at high risk for autism: Associations with initiating joint attention. *Autism Research*. Retrieved from http://onlinelibrary.wiley.com.proxy.library.vanderbilt.edu/doi/10.1002/aur.1623/full

Gillberg, C., & Coleman, M. (2000). The biology of the autistic syndromes. Cambridge University Press.

Gillberg, C., & Svennerholm, L. (1987). CSF monoamines in autistic syndromes and other pervasive developmental disorders of early childhood. *The British Journal of Psychiatry*, *151*(1), 89–94.

Gillberg, C., Svennerholm, L., & Hamilton-Hellberg, C. (1983). Childhood psychosis and monoamine metabolites in spinal fluid. *Journal of Autism and Developmental Disorders*, *13*(4), 383–396.

Graybiel, A. M. (2008). Habits, rituals, and the evaluative brain. *Annu. Rev. Neurosci.*, *31*, 359–387.

Guardia, D., Rolland, B., Karila, L., & Cottencin, O. (2011). GABAergic and glutamatergic modulation in binge eating: therapeutic approach. *Current Pharmaceutical Design*, *17*(14), 1396–1409.

Hamilton, P. J., Campbell, N. G., Sharma, S., Erreger, K., Hansen, F. H., Saunders, C., … others. (2013). De novo mutation in the dopamine transporter gene associates dopamine dysfunction with autism spectrum disorder. *Molecular Psychiatry*, *18*(12), 1315–1323.

Haznedar, M. M., Buchsbaum, M. S., Hazlett, E. A., LiCalzi, E. M., Cartwright, C., & Hollander, E. (2006). Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. *American Journal of Psychiatry*, *163*(7), 1252–1263.

Hettinger, J. A., Liu, X., Hudson, M. L., Lee, A., Cohen, I. L., Michaelis, R. C., … Holden, J. J. (2012). DRD2 and PPP1R1B (DARPP-32) polymorphisms independently confer increased risk for autism spectrum disorders and additively predict affected status in male-only affected sib-pair families. *Behavioral and Brain Functions*, *8*(1), 1.

Hogart, A., Nagarajan, R. P., Patzel, K. A., Yasui, D. H., & Lasalle, J. M. (2007). 15q11-13 GABAA receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. *Human Molecular Genetics*, *16*(6), 691–703. https://doi.org/10.1093/hmg/ddm014

Hollander, E., Anagnostou, E., Chaplin, W., Esposito, K., Haznedar, M. M., Licalzi, E., … Buchsbaum, M. (2005). Striatal Volume on Magnetic Resonance Imaging and Repetitive Behaviors in Autism. *Biological Psychiatry*, *58*(3), 226–232. https://doi.org/10.1016/j.biopsych.2005.03.040

Hommer, D. W., Knutson, B., Fong, G. W., Bennett, S., Adams, C. M., & Varner, J. L. (2003). Amygdalar recruitment during anticipation of monetary rewards. *Ann NY Acad Sci*, *985*, 476–8.

Honey, E., Leekam, S., Turner, M., & McConachie, H. (2007). Repetitive behaviour and play in typically developing children and children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(6), 1107–1115.

Hou, H., Jia, S., Hu, S., Fan, R., Sun, W., Sun, T., & Zhang, H. (2012). Reduced striatal dopamine transporters in people with internet addiction disorder. BioMed Research International, 2012.

Howard, J. S., Sparkman, C. R., Cohen, H. G., Green, G., & Stanislaw, H. (2005). A comparison of intensive behavior analytic and eclectic treatments for young children with autism. *Research in Developmental Disabilities*, *26*(4), 359–383.

Insel, T. R. (2003). Is social attachment an addictive disorder? *Physiology & Behavior*, *79*(3), 351–357. https://doi.org/10.1016/S0031-9384(03)00148-3

Karsten, A. M., & Carr, J. E. (2009). The effects of differential reinforcement of unprompted responding on the skill acquisition of children with autism. *Journal of Applied Behavior Analysis*, *42*(2), 327–334.

Kasari, C., Gulsrud, A. C., Wong, C., Kwon, S., & Locke, J. (2010). Randomized Controlled Caregiver Mediated Joint Engagement Intervention for Toddlers with Autism. *Journal of Autism and Developmental Disorders*, *40*(9), 1045–1056. https://doi.org/10.1007/s10803-010-0955-5

Kasari, C., Gulsrud, A., Paparella, T., Hellemann, G., & Berry, K. (2015). Randomized comparative efficacy study of parent-mediated interventions for toddlers with autism. *Journal of Consulting and Clinical Psychology*, *83*(3), 554–563. https://doi.org/10.1037/a0039080

Kim, J. H., & Lawrence, A. J. (2014). Drugs currently in Phase II clinical trials for cocaine addiction. *Expert Opinion on Investigational Drugs*, *23*(8), 1105–1122.

Kirsch, P., Reuter, M., Mier, D., Lonsdorf, T., Stark, R., Gallhofer, B., … Hennig, J. (2006). Imaging gene–substance interactions: the effect of the DRD2 TaqIA polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. *Neuroscience Letters*, *405*(3), 196–201.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, *59*(9), 809–816.

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, *12*(17), 3683–3687.

Kohls, G., Schulte-Rüther, M., Nehrkorn, B., Müller, K., Fink, G. R., Kamp-Becker, I., … Konrad, K. (2012). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, nss033.

Kryzak, L. A., Bauer, S., Jones, E. A., & Sturmey, P. (2013). Increasing responding to others' joint attention directives using circumscribed interests. *Journal of Applied Behavior Analysis*, *46*(3), 674–679. https://doi.org/10.1002/jaba.73

Kuhl, P. K., Conboy, B. T., Padden, D., Nelson, T., & Pruitt, J. (2005). Early speech perception and later language development: Implications for the" critical period". *Language Learning and Development*, *1*(3–4), 237–264.

Kumar, K., Sharma, S., Kumar, P., & Deshmukh, R. (2013). Therapeutic potential of GABAB receptor ligands in drug addiction, anxiety, depression and other CNS disorders. *Pharmacology Biochemistry and Behavior*, *110*, 174–184. https://doi.org/10.1016/j.pbb.2013.07.003

Lam, K. S., Bodfish, J. W., & Piven, J. (2008). Evidence for three subtypes of repetitive behavior in autism that differ in familiality and association with other symptoms. *Journal of Child Psychology and Psychiatry*, *49*(11), 1193–1200.

Langen, M., Bos, D., Noordermeer, S. D., Nederveen, H., van Engeland, H., & Durston, S. (2014). Changes in the development of striatum are involved in repetitive behavior in autism. *Biological Psychiatry*, *76*(5), 405–411.

Langen, M., Durston, S., Staal, W. G., Palmen, S. J., & van Engeland, H. (2007). Caudate nucleus is enlarged in high-functioning medication-naive subjects with autism. *Biological Psychiatry*, *62*(3), 262–266.

Langen, M., Schnack, H. G., Nederveen, H., Bos, D., Lahuis, B. E., de Jonge, M. V., … Durston, S. (2009). Changes in the developmental trajectories of striatum in autism. *Biological Psychiatry*, *66*(4), 327–333.

Lawrence, Y. A., Kemper, T. L., Bauman, M. L., & Blatt, G. J. (2010). Parvalbumin-, calbindin-, and calretinin-immunoreactive hippocampal interneuron density in autism. *Acta Neurologica Scandinavica*, *121*(2), 99–108.

Lepistö, T., Kujala, T., Vanhala, R., Alku, P., Huotilainen, M., & Näätänen, R. (2005). The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Research*, *1066*(1), 147–157.

Lifter, K., & Bloom, L. (1989). Object knowledge and the emergence of language. *Infant Behavior and Development*, *12*(4), 395–423.

Lin, A., Rangel, A., & Adolphs, R. (2012). Impaired Learning of Social Compared to Monetary Rewards in Autism. *Frontiers in Neuroscience*, *6*. https://doi.org/10.3389/fnins.2012.00143

Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., & Pickles, A. (2006). Autism from 2 to 9 years of age. *Archives of General Psychiatry*, *63*(6), 694–701.

Lovaas, O. I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of Consulting and Clinical Psychology*, *55*(1), 3.

Maestro, S., Muratori, F., Cavallaro, M. C., Pecini, C., Cesari, A., Paziente, A., … Palacio-Espasa, F. (2005). How young children treat objects and people: an empirical study of the first year of life in autism. *Child Psychiatry & Human Development*, *35*(4), 383–396.

Maestro, S., Muratori, F., Cavallaro, M. C., Pei, F., Stern, D., Golse, B., & Palacio-Espasa, F. (2002). Attentional skills during the first 6 months of age in autism spectrum disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(10), 1239–1245.

Mancil, G. R., & Pearl, C. E. (2008). Restricted Interests as Motivators: Improving Academic Engagement and Outcomes of Children on the Autism Spectrum. TEACHING Exceptional Children Plus, 4(6).

Marcus, R. N., Owen, R., Kamen, L., Manos, G., McQuade, R. D., Carson, W. H., & Aman, M. G. (2009). A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(11), 1110–1119.

McCauley, J. L., Olson, L. M., Delahanty, R., Amin, T., Nurmi, E. L., Organ, E. L., … Sutcliffe, J. S. (2004). A linkage disequilibrium map of the 1-Mb 15q12 GABA(A) receptor subunit cluster and association to autism. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *131B*(1), 51–59. https://doi.org/10.1002/ajmg.b.30038

McDougle, C. J., Scahill, L., Aman, M. G., McCracken, J. T., Tierney, E., Davies, M., … others. (2005). Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *American Journal of Psychiatry*, *162*(6), 1142–1148.

McElroy, S. L., Arnold, L. M., Shapira, N. A., Keck Jr, P. E., Rosenthal, N. R., Karim, M. R., … Hudson, J. I. (2003). Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *American Journal of Psychiatry*, *160*(2), 255–261.

Mendez, M. A., Horder, J., Myers, J., Coghlan, S., Stokes, P., Erritzoe, D., … Nutt, D. (2013). The brain GABA-benzodiazepine receptor alpha-5 subtype in autism spectrum disorder: A pilot [11 C] Ro15-4513 positron emission tomography study. *Neuropharmacology*, *68*, 195–201.

Menold, M. M., Shao, Y., Wolpert, C. M., Donnelly, S. L., Raiford, K. L., Martin, E. R., … Gilbert, J. R. (2001). Association analysis of chromosome 15 gabaa receptor subunit genes in autistic disorder. *Journal of Neurogenetics*, *15*(3–4), 245–259. https://doi.org/10.3109/01677060109167380

Mercier, C., Mottron, L., & Belleville, S. (2000). A psychosocial study on restricted interests in high functioning persons with pervasive developmental disorders. *Autism*, *4*(4), 406–425.

Minderaa, R. B., Anderson, G. M., Volkmar, F. R., Akkerhuis, G. W., & Cohen, D. J. (1989). Neurochemical study of dopamine functioning in autistic and normal subjects. *Journal of the American Academy of Child & Adolescent Psychiatry*, *28*(2), 190–194.

Mooney, E. L., Gray, K. M., Tonge, B. J., Sweeney, D. J., & Taffe, J. R. (2009). Factor analytic study of repetitive behaviours in young children with pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *39*(5), 765–774.

Morgan, L., Wetherby, A. M., & Barber, A. (2008). Repetitive and stereotyped movements in children with autism spectrum disorders late in the second year of life. *Journal of Child Psychology and Psychiatry*, *49*(8), 826–837.

Mori, T., Mori, K., Fujii, E., Toda, Y., Miyazaki, M., Harada, M., … Kagami, S. (2012). Evaluation of the GABAergic nervous system in autistic brain: 123 I-iomazenil SPECT study. *Brain and Development*, *34*(8), 648–654.

Nagaraj, R., Singhi, P., & Malhi, P. (2006). Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *Journal of Child Neurology*, *21*(6), 450–455.

Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., … others. (2010). Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Archives of General Psychiatry*, *67*(1), 59–68.

Narayan, M., Srinath, S., Anderson, G. M., & Meundi, D. B. (1993). Cerebrospinal fluid levels of homovanillic acid and 5-hydroxyindoleacetic acid in autism. *Biological Psychiatry*, *33*(8–9), 630–635.

Nefdt, N., Koegel, R., Singer, G., & Gerber, M. (2010). The use of a self-directed learning program to provide introductory training in pivotal response treatment to parents of children with autism. *Journal of Positive Behavior Interventions*, *12*(1), 23–32.

Nguyen, M., Roth, A., Kyzar, E. J., Poudel, M. K., Wong, K., Stewart, A. M., & Kalueff, A. V. (2014). Decoding the contribution of dopaminergic genes and pathways to autism spectrum disorder (ASD). *Neurochemistry International*, *66*, 15–26.

Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., … von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport*, *15*(5), 757–760.

Noble, E. P. (2000). Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: a review. *European Psychiatry*, *15*(2), 79–89. https://doi.org/10.1016/S0924-9338(00)00208-X

Noble, E. P., Noble, R. E., Ritchie, T., Syndulko, K., Bohlman, M. C., Noble, L. A., … Grandy, D. K. (1994). D2 dopamine receptor gene and obesity. *International Journal of Eating Disorders*, *15*(3), 205–217.

Oblak, A., Gibbs, T. T., & Blatt, G. J. (2009). Decreased GABAA receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. *Autism Research*, *2*(4), 205–219.

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2010). Decreased GABAB receptors in the cingulate cortex and fusiform gyrus in autism. *Journal of Neurochemistry*, *114*(5), 1414–1423.

Osterling, J. A., Dawson, G., & Munson, J. A. (2002). Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. *Development and Psychopathology*, *14*(02), 239–251.

Owen, R., Sikich, L., Marcus, R. N., Corey-Lisle, P., Manos, G., McQuade, R. D., … Findling, R. L. (2009). Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*, *124*(6), 1533–1540.

Ozonoff, S., Macari, S., Young, G. S., Goldring, S., Thompson, M., & Rogers, S. J. (2008). Atypical object exploration at 12 months of age is associated with autism in a prospective sample. *Autism*, *12*(5), 457–472.

Ozonoff, S., Pennington, B. F., & Rogers, S. J. (1991). Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *Journal of Child Psychology and Psychiatry*, *32*(7), 1081–1105.

Pandina, G. J., Bossie, C. A., Youssef, E., Zhu, Y., & Dunbar, F. (2007). Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *Journal of Autism and Developmental Disorders*, *37*(2), 367–373.

Pankert, A., Pankert, K., Herpertz-Dahlmann, B., Konrad, K., & Kohls, G. (2014). Responsivity to familiar versus unfamiliar social reward in children with autism. *Journal of Neural Transmission*, *121*(9), 1199–1210. https://doi.org/10.1007/s00702-014-1210-6

Parten, M. B. (1932). Social participation among pre-school children. *The Journal of Abnormal and Social Psychology*, *27*(3), 243.

Pascalis, O., & Kelly, D. J. (2009). The Origins of Face Processing in Humans: Phylogeny and Ontogeny. *Perspectives on Psychological Science*, *4*(2), 200–209. https://doi.org/10.1111/j.1745-6924.2009.01119.x

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual scanning of faces in autism. *Journal of Autism and Developmental Disorders*, *32*(4), 249–261.

Perry, R., Campbell, M., Adams, P., Lynch, N., Spencer, E. K., Curren, E. L., & Overall, J. E. (1989). Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. *Journal of the American Academy of Child & Adolescent Psychiatry*, *28*(1), 87–92.

Petry, N. M. (2006). Should the scope of addictive behaviors be broadened to include pathological gambling? *Addiction*, *101*(s1), 152–160.

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Archives of General Psychiatry*, *68*(1), 101–109.

Pierce, K., & Courchesne, E. (2001). Evidence for a cerebellar role in reduced exploration and stereotyped behavior in autism. *Biological Psychiatry*, *49*(8), 655–664.

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2015). Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated with Increased Symptom Severity. Biological Psychiatry.

Porter, N. (2012). Promotion of Pretend Play for Children with High-Functioning Autism Through the Use of Circumscribed Interests. *Early Childhood Education Journal*, *40*(3), 161–167. https://doi.org/10.1007/s10643-012-0505-1

Riby, D. M., & Hancock, P. J. (2008a). Viewing it differently: Social scene perception in Williams syndrome and autism. *Neuropsychologia*, *46*(11), 2855–2860.

Riby, D. M., & Hancock, P. J. B. (2008b). Do Faces Capture the Attention of Individuals with Williams Syndrome or Autism? Evidence from Tracking Eye Movements. *Journal of Autism and Developmental Disorders*, *39*(3), 421–431. https://doi.org/10.1007/s10803-008-0641-z

Rojas, D. C., Peterson, E., Winterrowd, E., Reite, M. L., Rogers, S. J., & Tregellas, J. R. (2006). Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. *BMC Psychiatry*, *6*(1), 1.

Ross, D. L., Klykylo, W. M., & Anderson, G. M. (1985). Cerebrospinal-fluid indoleamine and monoamine effects of fenfluramine treatment of infantile-autism. In Annals of Neurology (Vol. 18, pp. 394–394). Lippincott-Raven Publ 227 East Washington Sq, Philadelphia, PA 19106.

Salem, A. M., Ismail, S., Zarouk, W. A., Abdul Baky, O., Sayed, A. A., Abd El-Hamid, S., & Salem, S. (2013). Genetic variants of neurotransmitter-related genes and miRNAs in Egyptian autistic patients. The Scientific World JOURNAL, 2013.

Sallows, G. O., Graupner, T. D., & MacLean Jr, W. E. (2005). Intensive behavioral treatment for children with autism: Four-year outcome and predictors. *American Journal on Mental Retardation*, *110*(6), 417–438.

Sasson, N. J., Dichter, G. S., & Bodfish, J. W. (2012). Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PloS One*, *7*(8), e42457.

Sasson, N. J., Elison, J. T., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2011). Brief report: Circumscribed attention in young children with autism. *Journal of Autism and Developmental Disorders*, *41*(2), 242–247.

Sasson, N. J., & Touchstone, E. W. (2014). Visual attention to competing social and object images by preschool children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 584–592.

Sasson, N. J., Turner-Brown, L. M., Holtzclaw, T. N., Lam, K. S., & Bodfish, J. W. (2008). Children with autism demonstrate circumscribed attention during passive viewing of complex social and nonsocial picture arrays. *Autism Research*, *1*(1), 31–42.

Schmitz, N., Rubia, K., van Amelsvoort, T., Daly, E., Smith, A., & Murphy, D. G. M. (2008). Neural correlates of reward in autism. *The British Journal of Psychiatry: The Journal of Mental Science*, *192*(1), 19–24. https://doi.org/10.1192/bjp.bp.107.036921

Sears, L. L., Vest, C., Mohamed, S., Bailey, J., Ranson, B. J., & Piven, J. (1999). An MRI study of the basal ganglia in autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *23*(4), 613–624.

Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., … Wigler, M. (2007). Strong association of de novo copy number mutations with autism. *Science (New York, N.Y.)*, *316*(5823), 445–449. https://doi.org/10.1126/science.1138659

Shao, Y., Cuccaro, M. L., Hauser, E. R., Raiford, K. L., Menold, M. M., Wolpert, C. M., … Pericak-Vance, M. A. (2003). Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes. *American Journal of Human Genetics*, *72*(3), 539–548. https://doi.org/10.1086/367846

Shea, S., Turgay, A., Carroll, A., Schulz, M., Orlik, H., Smith, I., & Dunbar, F. (2004). Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*, *114*(5), e634–e641.

Shinohara, M., Mizushima, H., Hirano, M., Shioe, K., & others. (2004). Eating disorders with binge-eating behaviour are associated with the s allele of the 3'-UTR VNTR polymorphism of the dopamine transporter gene. *Journal of Psychiatry & Neuroscience: JPN*, *29*(2), 134.

Smilansky, S. (1968). The effects of sociodramatic play on disadvantaged preschool children.

Smith, C. J., Lang, C. M., Kryzak, L., Reichenberg, A., Hollander, E., & Silverman, J. M. (2009). Familial associations of intense preoccupations, an empirical factor of the restricted, repetitive behaviors and interests domain of autism. *Journal of Child Psychology and Psychiatry*, *50*(8), 982–990.

Smith, D. G., & Robbins, T. W. (2013). The Neurobiological Underpinnings of Obesity and Binge Eating: A Rationale for Adopting the Food Addiction Model. *Biological Psychiatry*, *73*(9), 804–810. https://doi.org/10.1016/j.biopsych.2012.08.026

Smith, I. M., Koegel, R. L., Koegel, L. K., Openden, D. A., Fossum, K. L., & Bryson, S. E. (2010). Effectiveness of a novel community-based early intervention model for children with autistic spectrum disorder. *American Journal on Intellectual and Developmental Disabilities*, *115*(6), 504–523.

Smith, K. S., Berridge, K. C., & Aldridge, J. W. (2011). Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. *Proceedings of the National Academy of Sciences*, *108*(27), E255–E264.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive Behavior Profiles in Asperger Syndrome and High-Functioning Autism. *Journal of Autism & Developmental Disorders*, *35*(2), 145–158.

Spezio, M. L., Adolphs, R., Hurley, R. S. E., & Piven, J. (2006). Abnormal Use of Facial Information in High-Functioning Autism. *Journal of Autism and Developmental Disorders*, *37*(5), 929–939. https://doi.org/10.1007/s10803-006-0232-9

Szatmari, P., Georgiades, S., Bryson, S., Zwaigenbaum, L., Roberts, W., Mahoney, W., … Tuff, L. (2006). Investigating the structure of the restricted, repetitive behaviours and interests domain of autism. *Journal of Child Psychology and Psychiatry*, *47*(6), 582–590.

Thompson, J., Thomas, N., Singleton, A., Piggot, M., Lloyd, S., Perry, E. K., … others. (1997). D2 dopamine receptor gene (DRD2) Taql A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics and Genomics*, *7*(6), 479–484.

Turner-Brown, L. M., Lam, K. S. L., Holtzclaw, T. N., Dichter, G. S., & Bodfish, J. W. (2011). Phenomenology and measurement of circumscribed interests in autism spectrum disorders. *Autism*, *15*(4), 437–456. https://doi.org/10.1177/1362361310386507

Tyacke, R. J., Lingford-Hughes, A., Reed, L. J., & Nutt, D. J. (2010). GABAB Receptors in Addiction and Its Treatment. In T. P. Blackburn (Ed.), Advances in Pharmacology (Vol. 58, pp. 373–396). Academic Press.

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W. (2016). Social Orienting and Attention Is Influenced by the Presence of Competing Nonsocial Information in Adolescents with Autism. *Frontiers in Neuroscience*, *10*.

Van der Geest, J. N., Kemner, C., Camfferman, G., Verbaten, M. N., & van Engeland, H. (2002). Looking at images with human figures: Comparison between autistic and normal children. *Journal of Autism and Developmental Disorders*, *32*(2), 69–75.

Van Der Geest, J. n., Kemner, C., Verbaten, M. n., & Van Engeland, H. (2002). Gaze behavior of children with pervasive developmental disorder toward human faces: a fixation time study. *Journal of Child Psychology and Psychiatry*, *43*(5), 669–678. https://doi.org/10.1111/1469-7610.00055

van Hulst, B. M., de Zeeuw, P., Bos, D. J., Rijks, Y., Neggers, S. F. W., & Durston, S. (2016). Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis. *Journal of Child Psychology and Psychiatry*, n/a-n/a. https://doi.org/10.1111/jcpp.12643

van Kooten, I. A., Palmen, S. J., von Cappeln, P., Steinbusch, H. W., Korr, H., Heinsen, H., … Schmitz, C. (2008). Neurons in the fusiform gyrus are fewer and smaller in autism. *Brain*, *131*(4), 987–999.

Vismara, L. A., & Lyons, G. L. (2007). Using Perseverative Interests to Elicit Joint Attention Behaviors in Young Children With Autism Theoretical and Clinical Implications for Understanding Motivation. *Journal of Positive Behavior Interventions*, *9*(4), 214–228. https://doi.org/10.1177/10983007070090040401

Vlachou, S., & Markou, A. (2010). GABAB Receptors in Reward Processes. In T. P. Blackburn (Ed.), *Advances in Pharmacology* (Vol. 58, pp. 315–371). Academic Press. Retrieved from http://www.sciencedirect.com/science/article/pii/S105435891058013X

Voelbel, G. T., Bates, M. E., Buckman, J. F., Pandina, G., & Hendren, R. L. (2006). Caudate nucleus volume and cognitive performance: Are they related in childhood psychopathology? *Biological Psychiatry*, *60*(9), 942–950.

Volkow, N. D., Ding, Y.-S., Fowler, J. S., Wang, G.-J., Logan, J., Gatley, J. S., … others. (1995). Is methylphenidate like cocaine?: Studies on their pharmacokinetics and distribution in the human brain. *Archives of General Psychiatry*, *52*(6), 456–463.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Hitzemann, R., … Pappas, N. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature*, *386*(6627), 830–833. https://doi.org/10.1038/386830a0

Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Franceschi, D., Maynard, L., … Swanson, J. M. (2002). Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in

extracellular dopamine: therapeutic implications. *Synapse (New York, N.Y.)*, *43*(3), 181–187. https://doi.org/10.1002/syn.10038

Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Logan, J., Childress, A.-R., … Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *The Journal of Neuroscience*, *26*(24), 6583–6588.

Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Logan, J., Childress, A.-R., … Wong, C. (2008). Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. *Neuroimage*, *39*(3), 1266–1273.

Watson, K. K., Miller, S., Hannah, E., Kovac, M., Damiano, C. R., Sabatino-DiCrisco, A., … Dichter, G. S. (2015). Increased reward value of non-social stimuli in children and adolescents with autism. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01026

Watt, N., Wetherby, A. M., Barber, A., & Morgan, L. (2008). Repetitive and stereotyped behaviors in children with autism spectrum disorders in the second year of life. *Journal of Autism and Developmental Disorders*, *38*(8), 1518–1533.

Werner, E., & Dawson, G. (2005). Validation of the phenomenon of autistic regression using home videotapes. *Archives of General Psychiatry*, *62*(8), 889–895.

Winsberg, B. G., Sverd, J., Castells, S., Hurwic, M., & Perel, J. M. (1980). Estimation of monoamine and cyclic-AMP turnover and aminoacid concentrations of spinal fluid in autistic children. Neuropediatrics, 11(03), 250–255.

Yip, J., Soghomonian, J.-J., & Blatt, G. J. (2007). Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta Neuropathologica*, *113*(5), 559–568. https://doi.org/10.1007/s00401-006-0176-3

Yip, J., Soghomonian, J.-J., & Blatt, G. J. (2008). Increased GAD67 mRNA expression in cerebellar interneurons in autism: implications for Purkinje cell dysfunction. *Journal of Neuroscience Research*, *86*(3), 525–530.

Young, K. S. (1998). Internet addiction: The emergence of a new clinical disorder. *CyberPsychology & Behavior*, *1*(3), 237–244.

Yun, I. A., Wakabayashi, K. T., Fields, H. L., & Nicola, S. M. (2004). The Ventral Tegmental Area Is Required for the Behavioral and Nucleus Accumbens Neuronal Firing Responses to Incentive Cues. *The Journal of Neuroscience*, *24*(12), 2923–2933. https://doi.org/10.1523/JNEUROSCI.5282-03.2004

Zeeland, S.-V., Ashley, A., Dapretto, M., Ghahremani, D. G., Poldrack, R. A., & Bookheimer, S. Y. (2010). Reward processing in autism. *Autism Research*, *3*(2), 53–67.

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. *International Journal of Developmental Neuroscience*, *23*(2), 143–152.

CHAPTER 2

SOCIAL ORIENTING AND ATTENTION IS INFLUENCED BY THE PRESENCE OF COMPETING NONSOCIAL INFORMATION IN ADOLESCENTS WITH AUTISM

Introduction

The Social Motivation Theory of Autism posits that autism spectrum disorder (ASD) is the result of an early and extreme lack of motivation toward social information, leading to the development of a social-specific reward deficit (Chevallier et al., 2012; Dawson, 1991; Dawson et al., 2005; Dawson and Lewy, 1989; Kohls et al., 2012) This theory provides an account of the social deficits that comprise ASD. Symptoms that are nonsocial in nature (e.g., restricted, repetitive patterns of behavior or interest) are also core features of ASD; however, the magnitude to which these nonsocial patterns of behavior occur is not accounted for within the framework of the social motivation theory.

A prominent feature of nonsocial symptoms in ASD is restricted, or circumscribed interests (CI). Commonly reported interests of individuals with ASD include vehicles, electronics, dinosaurs, particular animals, numbers, facts, cartoons, solitary games, and mechanical systems (Anthony et al., 2013; South et al., 2005; Turner-Brown et al., 2011) In contrast to the *reduced* reward processing associated with social motivation deficits in ASD, the excessive interest and fixation associated with CI, suggest a role for *increased* activity of reward circuitry in ASD. Further, it is possible that this enhanced experience of reward or pleasure associated with CI may bias attention away from social sources of stimulation. One hypothesis that can be considered from

this formulation is that a nonsocial attentional bias may contribute to reduced social interest and concomitant social deficits seen in ASD.

Typical patterns of attentional bias can be demonstrated using preferential viewing paradigms. The logic of this paradigm is that when images are paired, the resulting pattern of visual orientation and attention can give insight into the relative preference or reward value of the two stimulus types. Similar paradigms have been used to assess preference across species. For example, macaques show visual preference for their own species over others as young as two months of age (Kim et al., 1999). Similarly, human neonates show preference for both realistic and schematic human faces over non-face stimuli (Fantz, 1964; Goren, Sarty, & Wu, 1975; Johnson, Dziurawiec, Ellis, & Morton, 1991; Valenza, Simion, Cassia, & Umiltà, 1996). Previous studies of ASD have shown that the presence of CI stimuli alters patterns of visual attention. By measuring visual attention within arrays containing social and nonsocial (object) images, Sasson et. al (2008), showed that individuals with ASD explored fewer social images when they were paired with CI-related objects, compared to when social images were paired with neutral (non-CI-related) objects. In the current study, I used a preferential viewing paradigm to test the hypothesis that the presence of nonsocial stimuli biases attention in ASD and interferes with attention to social stimuli. Participants passively viewed arrays containing both social and object images; object images were varied between neutral, or "low autism interest" (LAI) images, and images associated with circumscribed interests, or "high autism interest" (HAI) images. I sought to measure both latency of initial choice as well as the distribution of overall preference patterns to social and nonsocial images. This paradigm allowed us to examine

whether social orientation and attention could be influenced by the presence of specific nonsocial images (e.g., CI-related objects).

Methods

Participants

Two groups of adolescents participated in this study: 48 with ASD (41 males, 7 females, mean age = 167.39 months, range = 116-218 months) and 39 who were typically developing (TD; 34 males, 5 females; mean age = 165.83 range = 111-227 months). All participants met the following general inclusion criteria: age between 9 and 18 years; intelligence quotient (IQ) greater than 70; absence of seizure disorder, acute medical, or genetic condition; and absence of any visual impairment uncorrectable with eyeglasses.

Participants with ASD were recruited through an autism research registry in conjunction with regional assessment and treatment clinical service programs for persons with ASD. Inclusion of the registry required a previous Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of ASD made by a licensed clinician experienced in the assessment and diagnosis of autism, and based on parent interview and direct observation for the completion standardized autism diagnostic assessment instruments (Autism Diagnostic Interview-Revised; ADI-R), Autism Diagnostic Observation Schedule; ADOS). Following referral from the registry, all ASD participants were evaluated by trained study personnel using (a) the ADI-R (Lord et al., 1994) to examine lifetime criteria for ASD, (b) the ADOS (Lord et al., 2012), (c) the Social Responsiveness Scale (SRS) (Constantino and Gruber, 2002) to examine the current severity of

autism symptoms, and (d) the Kaufman Brief Intelligence Test, Second Edition (KBIT-2) (Kaufman and Kaufman, 2004) to examine general cognitive ability.

TD children were recruited via an email sent university faculty and staff. TD children were excluded if they had a history of psychiatric or developmental disorder, if they were currently taking psychotropic medication, if an immediate family member had an ASD diagnosis, or if they received a score above the ASD cutoff on the SRS. These adolescents were chosen to be matched on gender and chronological age, compared to the ASD group. Groups were matched on gender because previous studies indicate interest in social stimuli and CI-related stimuli can vary between males and females (Sasson et al., 2012).

One TD participant was excluded for having an SRS score that fell in the ASD range. There was no significant difference between groups for nonverbal IQ ($t(62) = 1.60$, $p = .116$). Independent samples t-tests were conducted between groups for each of the psychometric measures and relevant subscales. As expected, ASD participants scored significantly higher than TD individuals on measures of social-communication and repetitive behavior. See Table 2.1 for group means and results of statistical analysis. Before participation, all individuals and their legal guardians supplied written informed consent for study participation. The protocol for this study was approved by the Vanderbilt University and the UNC-Chapel Hill School of Medicine Biomedical Institutional Review Boards.

Table 2.1 *Demographics and Participant Characterization for Study 1*

Characteristic	ASD (N = 33)	TD (N = 31)	t value (*p value*)
Age (years)	13.9 (4.0)	13.9 (3.0)	-.18 (*.857*)
Gender	29 M / 4 F	28 M / 3 F	--
Verbal IQ	98.9 (21.3)	112.5 (12.9)	3.11 (*.003*)
Nonverbal IQ	105.5 (16.7)	111.4 (12.6)	1.60 (*.116*)
Social Communication Questionnaire			
Total	20.7 (4.9)	3.0 (1.4)	-19.87 (< *.001*)
Social Responsiveness Scale			
T-Score	73.8 (8.6)	58.1 (4.4)	-9.17 (< *.001*)
Repetitive Behavior Scale—Revised			
Stereotyped Behavior	3.7 (2.4)	.1 (.5)	-8.21 (< *.001*)
Self-Injurious Behavior	2.0 (3.0)	.2 (.5)	-3.52 (*.001*)
Compulsive Behavior	4.2 (4.6)	.5 (1.5)	-4.35 (< *.001*)
Ritualistic Behavior	4.8 (4.0)	.6 (2.7)	-4.96 (< *.001*)
Total	7.2 (6.0)	1.2 (5.9)	-4.02 (< *.001*)
Interest Scale			
Number of Current Interests	10.3 (4.5)	9.6 (4.7)	-5.77 (*.566*)
Social Involvement	1.84 (.77)	1.03 (.80)	-4.10 (< *.001*)
Autism Diagnostic Observation Schedule			
Social + Communication	10.5 (3.5)	--	--
Stereotyped Behavior + Restricted Interests	4.0 (2.2)	--	--
Total Severity	14.5 (4.7)	--	--

ASD, Autism Spectrum Disorder; *TD*; typically developing; *M*, male; *F*; female

Stimuli and task

Preferential Viewing Task

The preferential viewing task was designed for this study and is comprised of 20 static, high-quality color picture arrays. Each array contained a pair of social and object images (see Figure 2.1). I chose to use static images to ensure greater experimental control across our stimulus categories, including accounting for category specific motion differences (e.g., biological vs. mechanical motion) as well as low-level salience properties of the stimuli, such as luminance and image complexity. Further, the use of these static images allowed us to include a contrast of low- and high- autism interest images based on previous experimental results.

The 20 social images were taken with permission from the MacArthur Foundation Research Network on Early Experience and Brain Development (Tottenham et al., 2009). Identities of the faces did not repeat, were split evenly between males and females, and consisted of Caucasian, African-American, and Asian-American. Of the 20 object stimuli, half were selected to represent items frequently occurring as topics of CI in ASD (South et al., 2005). Our lab has previously validated the reward value of these stimuli using standardized valence and arousal ratings. These stimuli were rated by participants with ASD as significantly higher in valence than control object images (Sasson et al., 2012). We have termed these CI-related stimuli "High Autism Interest" (HAI) objects. Examples of HAI objects include: trains, vehicles, airplanes, clocks, and blocks. The remaining objects included control objects, which were not related to CI and which we have found participants with ASD to rate significantly lower in valence (Sasson et al., 2012). We have termed these images "Low Autism Interest" (LAI) objects. Examples of LAI objects include: clothing, tools, musical instruments, and plants. Each image measured approximately 8 x 10 cm, and images were separated by a gap of approximately 12 cm. Images were also matched for

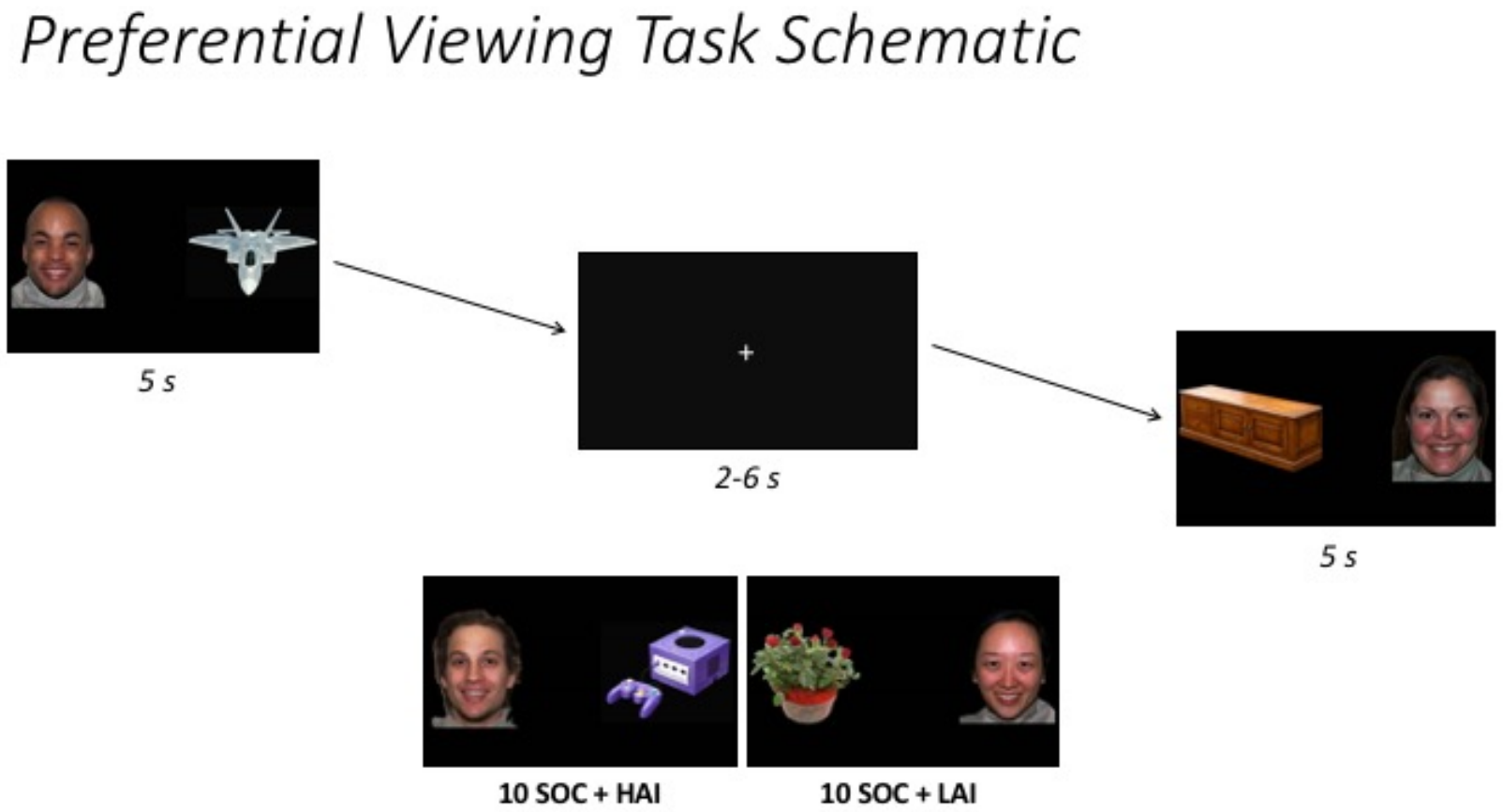

Figure 2.1 **Schematic of the preferential viewing task.** *SOC,* social; *HAI*, high autism interest

luminance and complexity. Equivalent areas of interest were drawn for social and nonsocial images, and each corresponded to approximately 25% of the total viewing area. Each stimulus array contained one social image paired with one object (either HAI or LAI) image. Positioning (left vs. right) of all stimulus categories was counterbalanced across arrays.

Eye-tracking

Testing occurred in a research laboratory. Participants sat approximately 60 cm from a 1,024 horizontal x 768 vertical 17-inch display and viewed stimuli subtending a visual angle of 16.1 degrees. Eye movements were recorded with a Tobii 1750 eye tracker (Tobii Technology, Stockholm, Sweden). The system uses an infrared light to produce reflection patterns on the corneas of the eye and monitors these reflections relative to the eye's position. This system samples at a rate of 50 Hz. This eye tracking system is mounted on the computer monitor, and therefore does not interfere with data collection. The system allows for head movement within a cubic space of 30x15x20 cm from a distance of 60 cm, allowing the participants to view in a naturalistic manner. The task was preceded by a 5-point calibration procedure, which was repeated until calibration was sufficient for each of the data points. Prior to the task, the participant was told to view the arrays however he/she wanted. Stimulus arrays were then displayed individually for 5 seconds each. Prior to each trial, a blank slide with a fixation cross appeared for 5 seconds to reorient attention and ensure that all scanning patterns began equidistant from each image in the stimulus pair.

Psychometric measures

Social Responsiveness Scale

The Social Responsiveness Scale (SRS; Constantino and Gruber, 2002) is a parent report questionnaire intended to measure behaviors related to social impairment, including social awareness, social information processing, capacity for reciprocal social communication, and social anxiety/avoidance, in children ages 4 to 18 years of age. An additional section of the SRS contains questions regarding autistic preoccupations and traits.

Autism Diagnostic Observation Schedule

The ADOS (Lord et al., 2012) is a semi-structured, play-based diagnostic measure of the core features of ASD. In addition to providing a score to measure against diagnostic thresholds, the ADOS now provides scores of ASD severity (Gotham et al., 2008). These scores can be used to compare severity across ages (ADOS modules) in individuals with ASD.

Repetitive Behavior Scale-Revised

Previous studies have shown a wide variety of repetitive behaviors occur in autism (Bodfish et al., 2000; Honey et al., 2007; Lam and Aman, 2007). I chose to use the Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al., 1999; Lam and Aman, 2007) to identify the presence of specific subtypes of repetitive behavior. The RBS-R is an informant rating scale that assesses five categories of repetitive behavior (motor stereotypy, repetitive self-injury, compulsions, routines/sameness, restricted interests). These subscales have high internal consistency, with Cronbach's alpha values ranging from .78 (restricted interests) to .91 (routines/sameness) (Lam and Aman, 2007).

Interest Scale

The Interest Scale (Turner-Brown et al., 2011) is used to collect detailed information on the presence and severity of circumscribed interests. This scale contains a checklist of interests, for which parents indicate if these are currently or have ever been an interest of their child; these are summed separately to indicate the number of past interests and number of current interests the child has endorsed. Additional questions characterize the child's strongest interest, including the degree to which this interest is shared with other people (social involvement), and the flexibility, frequency, intensity, interference, and accommodation of that specific interest, which are combined to produce a total severity score (range 0-23; higher score indicates greater severity).

Analysis of task performance

The nature of the paired preference task requires that each participant is looking at the slide for a sufficient amount of time to observe both images. Therefore, I developed a method to exclude participants based on insufficient total look time per slide, as to eliminate potential bias from the data. To calculate exclusion criteria, each participant was judged based on how many slides they viewed for less than 2.5 seconds (half the total time each stimulus was presented). Each participant who scored higher than 10 was excluded from analyses. Applying these criteria resulted in exclusion of 15 participants with ASD and 7 TD participants. Analysis revealed that the excluded group did not differ from the included group on age ($t(84) = 1.24$, $p = .217$) or nonverbal IQ ($t(82) = .507$, $p = .613$); however, the excluded group contained significantly more females than those included in final analyses.

Eye-tracking variables

Eye-tracking data was analyzed to look at a variety of gaze components. These variables were averaged across social images and object images, within array types, resulting in four dependent variable categories for each eye-tracking variable: SOC + LAI: Social, SOC + HAI: Social, SOC + LAI: Object, and SOC + HAI: Object. Eye tracking patterns were analyzed as a result of conducting fixation analyses. Fixations were classified using the Tobii Studio I-VT filter, which defines fixations as gaze moving at a velocity slower than 30 degrees per second, for at least 60 milliseconds. Four dependent variables were extracted from the data collected: (a) Preference: the proportion of on screen fixation time devoted to each image type, relative to total time spent on the stimulus array; (b) Detail orientation: the average number of discrete fixations the participant makes on each stimulus type, relative to total time on the image, across arrays; (c) Fixation duration: the average length of fixations to each image type, across arrays; and (d) Prioritization: the latency to first fixate on each stimulus type, which measures attention capture and orienting.

Statistical analysis

Repeated measures analysis of variance (RM-ANOVA) was conducted on each of the primary variables, with object type (LAI or HAI) as the within-subjects variable and group (TD, ASD) as the between groups variable. A significant interaction for any of the dependent variables would suggest that one object type disproportionately influences attention, compared to the other. All significant interactions were followed up with post-hoc analyses to identify the direction of the effect. Separate RM-ANOVA analyses were conducted for variables pertaining to social attention and object attention.

Bivariate (Pearson's r) correlations were used to assess relationships between eye-tracking and psychometric data. For these analyses, each variable was log-transformed to account for skewness in the distributions and to improve interpretability. Each variable was transformed by a factor of log(x+1) to preserve data points equal to zero, which were meaningful in this ratio data set.

Results

Figure 2.2 illustrates the differences in relative look time between the two groups; red indicates more time spent looking to the region, while yellow indicates less looking. Aggregated viewing time of the TD group indicates more time spent looking to social images (Figure 2.2b), while aggregated viewing time of the ASD group indicates greater looking to the object images (Figure 2.2c).

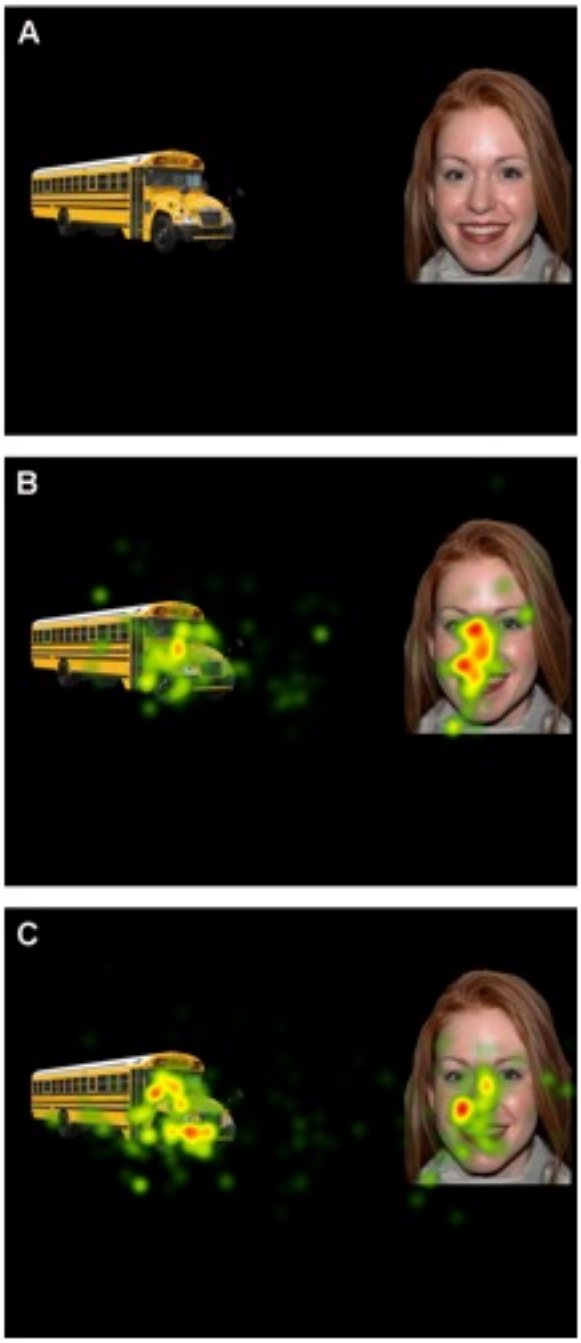

Figure 2.2 **Sample array and heat maps for ASD and TD participants**
Viewing time differed across participant groups for social and object images. **(A)** Sample preferential viewing array (SOC + HAI). **(B)** Aggregated viewing time for TD participants. **(C)** Aggregated viewing time for ASD participants. Regions marked in red indicate the greatest amount of viewing time. *ASD,* Autism Spectrum Disorder; *TD*, typically developing; *SOC*, social; *HAI*, high autism interest

Group differences: Eye-tracking variables

Preference - Social

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) Repeated measures (RM)-ANOVA was conducted for social preference. There was no group x array interaction ($p = .184$). There was a main effect of array ($F(1, 62) = 25.32$, $p < .0001$). There was a main effect of group ($F(1, 62) = 21.14$, $p < .0001$). Main effect results indicate both groups showed greater preference for faces in SOC + LAI arrays, compared to SOC + HAI arrays. Additionally, the TD group showed greater total fixation time for faces than the ASD group in both array types. Figure 2.3a illustrates group differences for social preference.

Preference – Object

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for object preference. There was no group x array interaction ($p = .164$). There was a main effect of array ($F(1, 62) = 34.90$, $p < .0001$). There was a main effect of group ($F(1, 62) = 7.95$, $p < .01$). Main effect results indicate both groups showed greater preference for objects in SOC + HAI arrays, compared to SOC + LAI arrays. Additionally, the ASD group showed greater total fixation time for objects than the TD group in both array types. Figure 1.3b illustrates group differences for object preference.

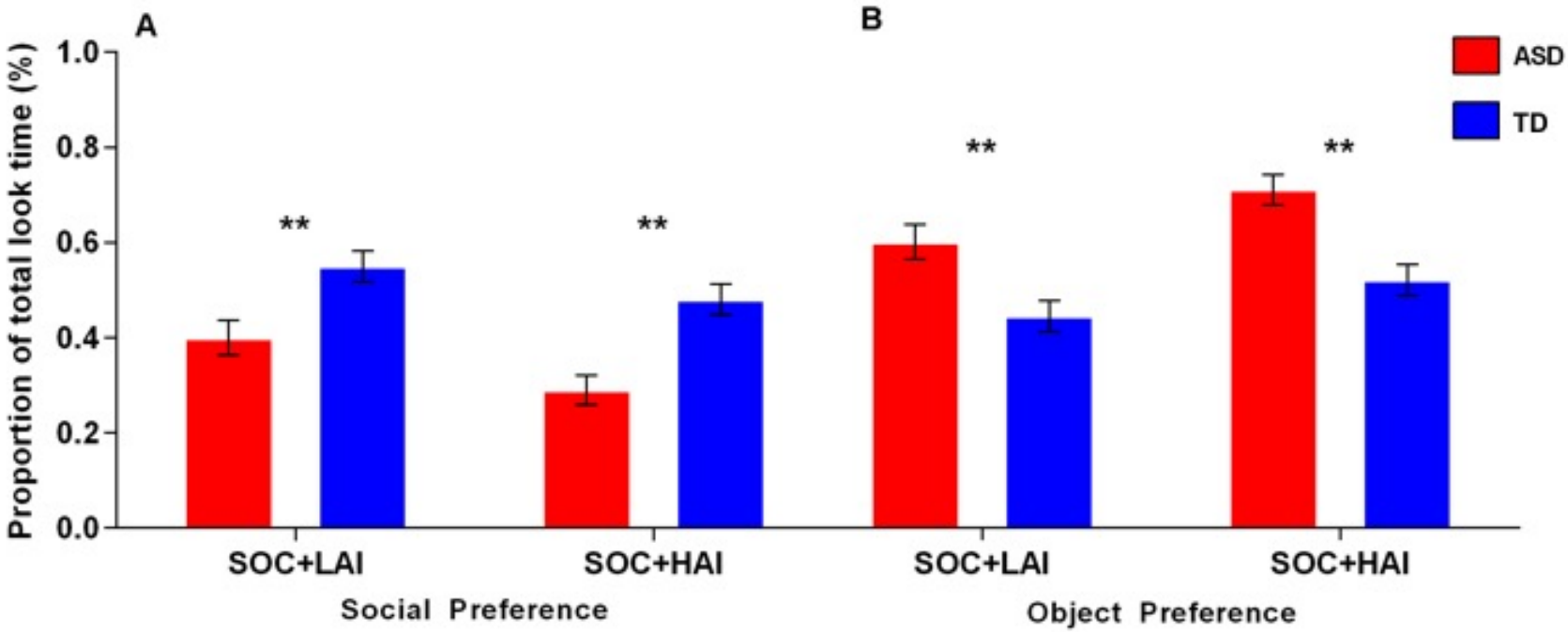

Figure 2.3 **Average proportion of total look time for social and object images in ASD and TD participants.**
(A) Proportion of look time to social images and **(B)** proportion of look time to object images. Error bars indicate standard error of the mean. **, $p < .01$; *ASD,* Autism Spectrum Disorder; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Detail Orientation – Social

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for the number of fixations on social images. There was no group x array interaction ($p = .30$). There was a main effect of array ($F(1, 62) = 8.29$, $p = .005$) and group ($F(1, 62) = 12.75$, $p = .001$). These results indicate that both groups made more fixations to social images when paired with HAI images than when paired with LAI images; the ASD group made significantly more fixations on social images than TYP, in both contexts.

*Detail Orientation – Objec*t

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for the number of fixations on object images. There was no group x array interaction ($p = .24$). The main effect of array was at trend-level significance ($F(1, 62) = 1.40$, $p = .056$). These results indicate that both groups made more fixations to LAI images than HAI images. There was no main effect of group ($p = .735$).

Fixation Duration – Social

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for the average fixation duration on social images. There was no group x array interaction ($p = .156$). There was a main effect of array ($F(1, 62) = 5.77$, $p = .019$). There was also a main effect of group ($F(1, 62) = 17.81$, $p < .0001$). These results indicate that both groups made longer fixations, on average, to faces in SOC + LAI arrays, compared to SOC + HAI arrays. Additionally, TD participants made longer fixations to social images in both conditions, compared to ASD. Post-hoc paired samples t-test showed that for the ASD group only, fixations

to social images were significantly shorter in duration when paired with HAI objects, compared to LAI objects ($t(32) = 28.05$, $p = .008$). Group differences are illustrated in Figure 2.4.

Fixation Duration – Object

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for the average fixation duration on object images. There was no group x array interaction ($p = .63$). There was no main effect of array ($p = .26$) or group ($p = .85$). These results indicate that the average length of fixation did not differ based on group or object type.

Prioritization – Social

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for latency to first fixation for social images. A group x array interaction was at trend-level significance ($F(1, 62) = 3.58$, $p = .063$). There was a main effect of array ($F(1, 62) = 5.23$, $p = .026$), and a trend-level main effect of group ($F(1, 62) = 3.44$, $p = .068$). These results indicate that both groups looked at faces more quickly when faces were paired with LAI objects, compared to HAI objects. The trend-level interaction and group effects suggest this main effect of array is driven by the ASD group showing larger differences in face latency between arrays than the TD groups. Post-hoc paired-samples t-tests show that for the ASD group only, latency to face is significantly slower when faces are paired with HAI objects, compared to LAI objects ($t(32) = -2.53$, $p = .02$). Figure 2.5 illustrates prioritization differences between groups.

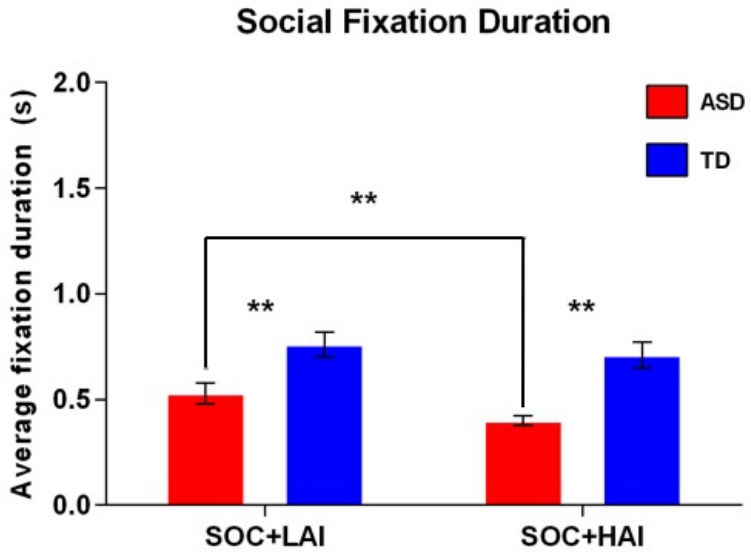

Figure 2.4 **Average fixation duration to social and object images in ASD and TD participants.** Error bars indicate standard error of the mean; **, $p < .01$; ASD, Autism Spectrum Disorder; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

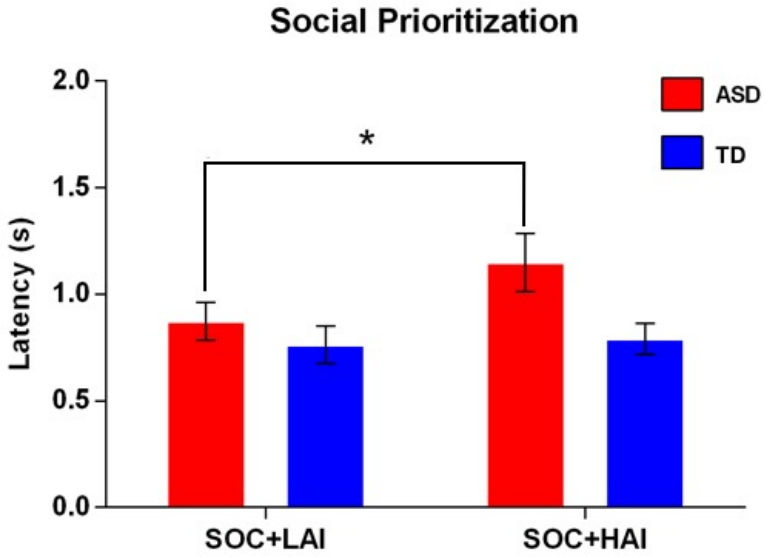

Figure 2.5 **Average latency to first fixate on social images in ASD and TD participants.** Error bars indicate standard error of the mean; *, $p < .05$; ASD, Autism Spectrum Disorder; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Prioritization – Object

A 2x2 (Group: ASD, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for latency to first fixation for object images. The group x array interaction was not significant (p = .22). There was no main effect of array (p = .574), but the main effect of group showed a trend toward significance ($F(1, 62) = 3.58$, p = .06). These results indicate the ASD group looked more quickly to both object types than TD.

Correlations: Eye-tracking variables and psychometric measures

One additional ASD participant was excluded for psychometric correlational analyses due to missing data on the psychometric variables of interest. All correlation analyses were performed using log-transformed variables, as previously described. The following correlations were conducted using data from the ASD group only.

First, correlations were calculated between autism severity and specific eye-tracking variables. These variables included all those where group differences were found between ASD and TD groups: social and object preference, social detail orientation, social fixation duration, and social prioritization. Pearson correlation analyses revealed significant correlations between number of total current interests, as measured by the Interest Scale, and both the face and object preference variables. For SOC + HAI arrays, ASD participants who had a greater number of interests, spent significantly less time looking at face images (r = -.60, p < .001; Figure 1.6a) and more time looking at object images (r = .35, p = .048; Figure 1.6b). This relationship was not seen in SOC + LAI arrays for either face (r = -.33, p = .06) or object (r = .008, p = .97) images. I also examined the relationship between face and object preference in SOC + HAI arrays and the SRS,

with the items relating to repetitive behavior removed. This revealed no relationship for either face preference (r = - .07, p = .69; Figure 1.6c) or object preference (r = -.08, p = .66; Figure 1.6d). There were no other significant correlations found between the remaining eye-tracking variables and any psychometric measures.

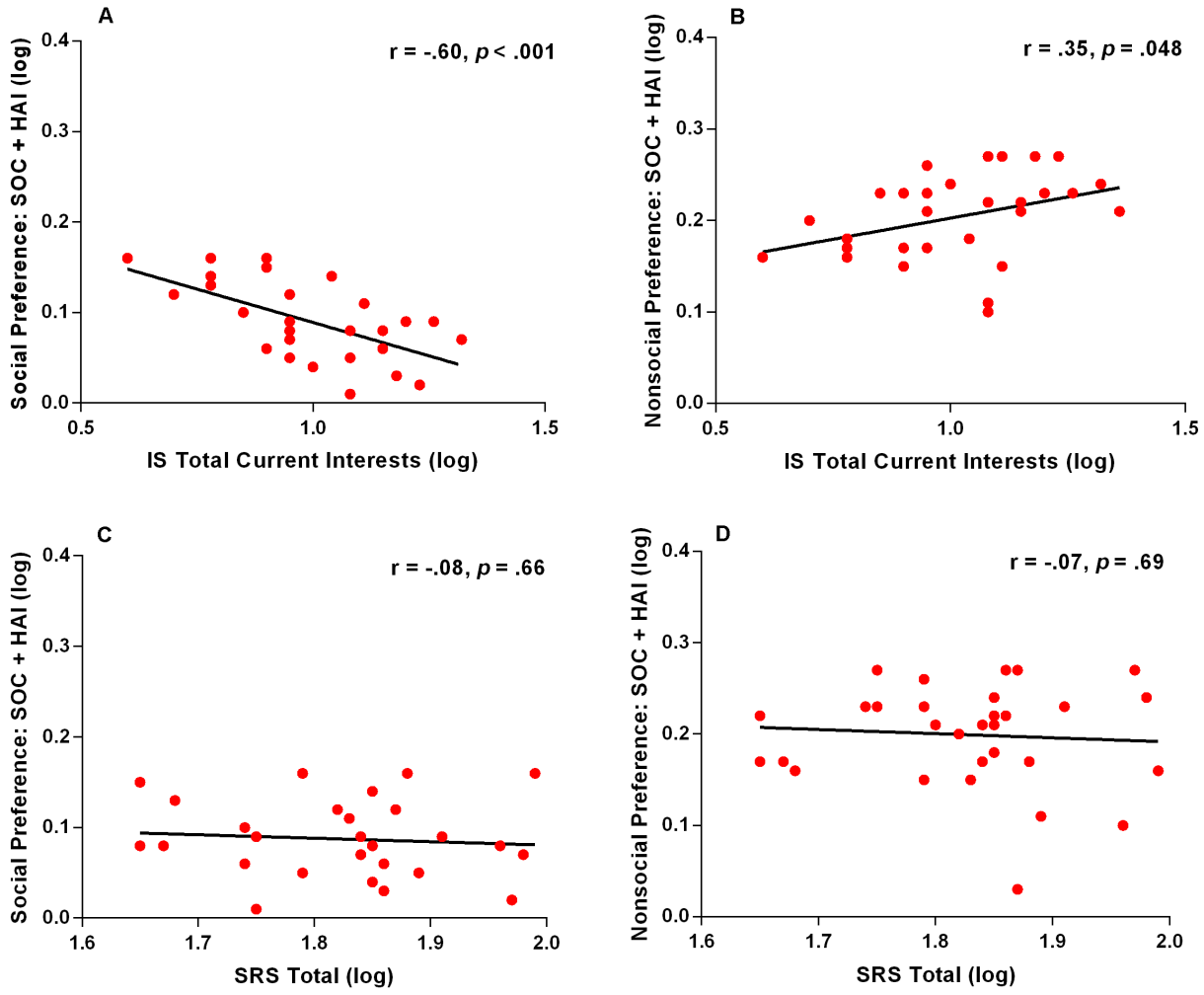

Figure 2.6 **Correlation between eye-tracking variables and phenotype measures for ASD participants.**
(A) Correlation of social preference and total number of current interests; **(B)** Correlation of nonsocial preference and total number of current interests; **(C)** Correlation of social preference and total score on the SRS; **(D)** Correlation of nonsocial preference and total score on the SRS. *ASD,* Autism Spectrum Disorder; *SOC*, social; *HAI*, high autism interest; *IS*, Interest Scale; *SRS*, Social Responsiveness Scale

Discussion

The purpose of the current study was to assess visual preference and gaze dynamics to social and nonsocial stimuli in adolescents with ASD, compared to typically developing peers. Group differences were assessed using a preferential viewing task, which paired social images with either neutral or CI-related object images. Overall, individuals with ASD preferred to look at object images (both LAI and CI-related), while TD adolescents preferred to look at faces. Groups differed in their prioritization of social information, such that TD adolescents displayed a shorter latency to fixate on social images than those with ASD.

I hypothesized that social viewing in ASD may be specifically influenced by the presence of certain types of nonsocial images, such as those related to CI. This was true for two variables: social latency and social fixation duration. Individuals with ASD displayed a longer latency to orient to faces when they were paired with HAI images than LAI images. Importantly, groups did not differ in latency to orient to faces when they were paired with LAI images. It is also worth noting that social preference was reduced in the presence of HAI images, compared to LAI images; however, this was true for both ASD and TD participants. Together, these findings provide support for our hypothesis and suggest social attention in ASD may be uniquely influenced by particular pieces of nonsocial information. Our findings are in line with previous studies that have found enhanced viewing of nonsocial objects by persons with ASD (Elison et al., 2012; Klin et al., 2002; Sasson et al., 2008, 2011). A recent study of preferential viewing in young children with ASD also revealed similar patterns of attention, suggesting this enhanced nonsocial viewing may be stable throughout childhood and adolescents (Sasson and Touchstone,

2014). Together, these studies highlight the potential importance of examining how opportunities for social experience can be diminished by the presence of competing nonsocial experiences.

Unlike the previously mentioned findings, detail orientation did not seem to follow the same pattern as the other eye-tracking variables. Participants made more, but shorter, fixations to social images when these images were paired with HAI objects, compared to LAI objects and this pattern was more pronounced for participants with ASD than TD. This pattern was not found for the number or duration of fixations to object images. These results align with a previous study of social + nonsocial visual arrays, which found increased detail orientation in ASD compared to TD adolescent peers (Sasson et al., 2008). However, while non-significant, these data trended toward increased detail orientation for object images, rather than social.

The core feature of unusual or circumscribed interests in ASD is closely linked conceptually with the kind of nonsocial preference found in the present study. The term circumscribed or restricted interest in ASD is often assumed clinically to represent a restriction or decrease in the number of interests in ASD relative to typically developing peers. However, no significant difference was found between groups for the number of interests endorsed on the Interest Scale, in line with previous studies of CI in ASD (Anthony et al., 2013; Turner-Brown et al., 2011). Also in line with the findings of previous studies, participants in our ASD sample endorsed interests that were more nonsocial in content than their TD peers and more frequently engaged in their primary interest in solitude, while TD peers more frequently engaged in their primary interest socially. These findings highlight the nonsocial nature of interests in ASD and help elucidate the association found between social viewing in the context of HAI images and CI severity (as

measured by the Interest Scale) in our ASD sample. A preference for viewing nonsocial over social images during the paired preference task was associated with a greater amount of nonsocial interests in our ASD sample. This correlation may represent a relationship between atypicality of interest and stimulus preference in ASD.

The current study found deficits in social orientation and attention in participants with ASD, including decreased preference, decreased duration of fixation, and increased latency to view social images, compared to TD peers. These results are consistent with the Social Motivation Theory of Autism (Chevallier et al., 2012; Dawson et al., 2005; Kohls et al., 2012). I also found evidence of enhanced nonsocial preference in individuals with ASD, indicated by increased preference for object images and decreased latency to fixate on object images, compared to TD peers. Enhanced nonsocial motivation has been found in individuals with ASD using behavioral measures (Damiano et al., 2012; Sasson et al., 2012; Watson et al., 2015) and other eye-tracking paradigms (Elison et al., 2012; Sasson et al., 2008, 2011; Sasson and Touchstone, 2014). These object preference findings are important to consider in light of neuroimaging studies that show enhanced activation of reward circuitry in ASD in response to nonsocial information (Cascio et al., 2014; Dichter et al., 2012). I also found evidence that decreased social attention may be related to increases in nonsocial preference in ASD. Taken together, these studies of object preference suggest that motivational differences in ASD include both nonsocial and social sources of motivation and reward. Such a pattern indicates that an expanded version of the social motivation conceptual model of ASD may be more appropriate. A broader motivational model may account for both social impairments and restricted repetitive behaviors, as well as the potential inter-relationships between these two core ASD domains. From a motivational

perspective, the potential for social and nonsocial sources of stimulation to compete for attention and effort in ASD suggests a more dynamic relationship between these sources of reward.

The phenomenon of increased motivation toward one type of stimulation contributing to decreased motivation for another source of stimulation has been termed "motivational toxicity" (Bozarth, 1994). This effect has been found in other clinical contexts such as substance abuse (e.g., Esch and Stefano, 2004), some types of disordered eating (e.g., Smith and Robbins, 2013), and non-drug form of addiction such as compulsive internet use (e.g., Young, 1998) or gambling (e.g., Petry, 2006). In these contexts, as behavior related to the focus of the compulsion or addiction increases (e.g., drug intake, compulsive eating patterns, internet use) there is a corresponding reduction in the reward value of other forms of activity such as social relationships, vocational activities, and pursuit of other hobbies. Often, it is this secondary loss of reward value of more healthy or adaptive activities that contributes to functional impairment in these conditions (Bozarth, 1994). Given this motivational toxicity framework that can account for experience-dependent changes in motivation over time, it is interesting to note previous findings in ASD of diminished substance abuse (e.g., Bejerot and Nylander, 2003; Chaplin et al., 2011; Mangerud et al., 2014; Santosh and Mijovic, 2006), restricted food preferences (e.g., Bandini et al., 2010; Cermak et al., 2010; Emond et al., 2010; Schreck et al., 2004; Schreck and Williams, 2006), and increased drive for internet use (e.g., Kuo et al., 2014; MacMullin et al., 2015; Mazurek et al., 2011; Shane-Simpson et al., 2016). One hypothesis that emerges from this dynamic motivational framework is that several seemingly disparate aspects of the autism phenotype (e.g., social deficits, restricted interests, picky eating, special abilities) may be related to underlying deficits in motivation and reward function in ASD.

One potential criticism of the current study was our choice to use static, rather than dynamic stimuli. Static images were chosen for four reasons. First, static images were chosen to increase our ability to exert control over low-level properties of the social and nonsocial stimulus pairs (e.g. visual angle, luminance, contrast, intensity, and orientation). Previous studies have found that individuals with ASD may process visual information differently from their typically developing peers, including superior performance on visual detail-oriented tasks (Kemner et al., 2008; Mottron et al., 2006; O'Riordan, 2004; O'Riordan et al., 2001; O'Riordan and Plaisted, 2001; Plaisted et al., 1998) and attention that is differentially driven by low-level stimulus properties relative to typically developing peers (Amso et al., 2014). Thus matching our social and nonsocial stimuli on these features helps ensure that any stimulus-type difference in attention between groups is not simply a function of low-level processing advantage in ASD. This degree of salience matching is not possible when using more complex visual stimuli like movies, and thus use of dynamic stimuli in an effort to increase ecological validity represents an important trade-off between potential validity and experimental control. Second, across the previously published studies of eye-tracking in ASD a uniform finding has been atypicalities in attentional parameters associated with social stimuli and this has been found for both static (Anderson et al., 2006; Elison et al., 2012; McPartland et al., 2011; Pelphrey et al., 2002; Sasson et al., 2008, 2011; Sasson and Touchstone, 2014) and dynamic stimuli (Chevallier et al., 2015; Jones and Klin, 2013; Klin et al., 2002, 2009; Klin and Jones, 2008; Pierce et al., 2011, 2015). Thus it is clear that the kind of diminished attention to social stimuli found in the present study is consistent with similar findings in previous studies of both dynamic and static displays. Therefore, while the nature of stimulus presentation (static/dynamic) may alter the level or

amount of attention obtained (e.g., more attention paid to dynamic stimuli), it does not appear to alter the relative differences in attention to social versus nonsocial images that is the focus of this study. Third, static visual image viewing has been repeatedly shown to elicit widespread neural activation outside of the visual cortex similar to viewing of dynamic images, and this has been shown to be the case for both social and nonsocial stimuli. For example, perception of static faces has been shown to increase activity in brain regions associated with emotion, reward, spatial perception, and motion processing (Haxby et al., 2002). Similarly, viewing static images of tools can elicit increased activity in motion and motor planning areas of the brain, compared to other object categories, such as animals (e.g., Chao et al., 1999). These studies suggest that across image categories, viewing static images is sufficient to recruit activation in brain regions similar to those that would show enhanced activity during actual use of objects or social interaction. Finally, it is not necessarily the case that viewing static images is not ecologically valid, particularly in the realm of operationalizing preference or choice. There are a variety of contexts in which people do choose to view pictures (e.g., children's story books, museums). This is perhaps most notable regarding use of the internet, where social media platforms such as Instagram and Facebook largely revolve around viewing static images.

Another limitation of our image set is that they were not matched in familiarity between social and nonsocial; faces were of strangers, but objects were items with which participants may have had regular interactions. However, it is important to consider that this relative difference in familiarity of faces and objects would be true for both groups: faces were novel for both ASD and typically developing participants, just as objects were likely familiar. Thus, it is unlikely that familiarization alone could account for the clear differences observed between groups. It is

possible that inclusion of familiar social images (e.g., faces of family members) may have elicited enhanced social attention in participants with ASD, although this has not been observed in previous studies (Dalton et al., 2005; Gillespie-Smith et al., 2014; Sterling et al., 2008). Likewise, it is important to note that our HAI stimuli were also not individualized to be the most salient or familiar object for each ASD participant in relation to his or her own idiosyncratic circumscribed interest. Thus, although the unfamiliar faces may have contributed to some degree of overestimation of deficits in social attention in the ASD group, the use of non-individualized CI images also likely underestimated the degree to which nonsocial attention was biased in the ASD group. Previous studies of ASD have used nonsocial stimuli that are specific to an individual's circumscribed interest (e.g., Cascio et al., 2014; Foss-Feig et al., 2016). In contrast, our method allows us to examine the effect of general stimulus categories (social versus nonsocial). Indeed, it is remarkable that even nonsocial images outside of a person with autism's very idiosyncratic circumscribed interest were still capable of biasing his or her attention. The presence of this more general nonsocial preference points out that object bias in ASD may extend beyond just individualized areas of interest. Further, it suggests that a generalized bias to attend to and engage with nonsocial, rather than social, sources of stimulation may set the stage for the later development and refinement of a more idiosyncratic nonsocial circumscribed interest.

These results add to previous literature that has found enhanced nonsocial preference in ASD) and extends this body of evidence by showing that the presence of nonsocial information can alter social orientation and attention in adolescents with ASD. These findings suggest a more complex pattern of motivational influences in autism than is suggested by the social motivation

hypothesis: both diminished social motivation *and* increased nonsocial motivation may contribute to the development of ASD in general and to ASD-associated atypicalities in attention and subsequent information processing in particular.

REFERENCES

Amso, D., Haas, S., Tenenbaum, E., Markant, J., & Sheinkopf, S. J. (2014). Bottom-up attention orienting in young children with autism. *Journal of Autism and Developmental Disorders*, *44*(3), 664–673.

Anderson, C. J., Colombo, J., & Jill Shaddy, D. (2006). Visual scanning and pupillary responses in young children with autism spectrum disorder. *Journal of Clinical and Experimental Neuropsychology*, *28*(7), 1238–1256.

Anthony, L. G., Kenworthy, L., Yerys, B. E., Jankowski, K. F., James, J. D., Harms, M. B., … Wallace, G. L. (2013). Interests in high-functioning autism are more intense, interfering, and idiosyncratic than those in neurotypical development. *Development and Psychopathology*, *25*(03), 643–652.

Bandini, L. G., Anderson, S. E., Curtin, C., Cermak, S., Evans, E. W., Scampini, R., … Must, A. (2010). Food selectivity in children with autism spectrum disorders and typically developing children. *The Journal of Pediatrics*, *157*(2), 259–264.

Bejerot, S., & Nylander, L. (2003). Low prevalence of smoking in patients with autism spectrum disorders. *Psychiatry Research*, *119*(1), 177–182.

Bodfish, J., Symons, F., & Lewis, M. (1999). The repetitive behavior scale. *Western Carolina Center Research Reports*.

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders*, *30*(3), 237–243.

Bozarth, M. A. (1994). Pleasure systems in the brain. In *Pleasure: The politics and the reality, Wiley* (p. 5–14 +refs). New York: John Wiley & Sons.

Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P., … Cao, A. (2014). Affective neural response to restricted interests in autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*(2), 162–171.

Cermak, S. A., Curtin, C., & Bandini, L. G. (2010). Food selectivity and sensory sensitivity in children with autism spectrum disorders. *Journal of the American Dietetic Association*, *110*(2), 238–246.

Chao, L. L., Haxby, J. V., & Martin, A. (1999). Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects. *Nature Neuroscience*, *2*(10), 913–919. https://doi.org/10.1038/13217

Chaplin, E., Gilvarry, C., & Tsakanikos, E. (2011). Recreational substance use patterns and co-morbid psychopathology in adults with intellectual disability. *Research in Developmental Disabilities*, *32*(6), 2981–2986.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*(4), 231–239.

Chevallier, C., Parish-Morris, J., McVey, A., Rump, K. M., Sasson, N. J., Herrington, J. D., & Schultz, R. T. (2015). Measuring social attention and motivation in autism spectrum disorder using eye-tracking: Stimulus type matters. *Autism Research*, *8*(5), 620–628. https://doi.org/10.1002/aur.1479

Constantino, J. N., & Gruber, C. P. (2002). The social responsiveness scale. *Los Angeles: Western Psychological Services*.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., … Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, *8*(4), 519–526.

Damiano, C. R., Aloi, J., Treadway, M., Bodfish, J. W., & Dichter, G. S. (2012). Adults with autism spectrum disorders exhibit decreased sensitivity to reward parameters when making effort-based decisions. *Journal of Neurodevelopmental Disorders*, *4*, 13. https://doi.org/10.1186/1866-1955-4-13

Dawson, G. (1991). VIII A Psychobiological Perspective on the Early Socio-emotional Development of Children with Autism. *Models and Integrations*, *3*, 207.

Dawson, G., & Lewy, A. (1989). Arousal, attention, and the socioemotional impairments of individuals with autism. Retrieved from http://psycnet.apa.org.proxy.library.vanderbilt.edu/psycinfo/1989-97258-003

Dawson, G., Webb, S. J., Wijsman, E., Schellenberg, G., Estes, A., Munson, J., & Faja, S. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology*, *17*(03), 679–697.

Dichter, G. S., Felder, J. N., Green, S. R., Rittenberg, A. M., Sasson, N. J., & Bodfish, J. W. (2012). Reward circuitry function in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *7*(2), 160–172.

Elison, J. T., Sasson, N. J., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2012). Age trends in visual exploration of social and nonsocial information in children with autism. *Research in Autism Spectrum Disorders*, *6*(2), 842–851.

Emond, A., Emmett, P., Steer, C., & Golding, J. (2010). Feeding symptoms, dietary patterns, and growth in young children with autism spectrum disorders. *Pediatrics*, *126*(2), e337–e342.

Esch, T., & Stefano, G. B. (2004). The neurobiology of pleasure, reward processes, addiction and their health implications. *Neuroendocrinology Letters*, *25*(4), 235–251.

Fantz, R. L. (1964). Visual Experience in Infants: Decreased Attention to Familiar Patterns Relative to Novel Ones. *Science*, *146*(3644), 668–670. https://doi.org/10.1126/science.146.3644.668

Foss-Feig, J. H., McGugin, R. W., Gauthier, I., Mash, L. E., Ventola, P., & Cascio, C. J. (2016). A functional neuroimaging study of fusiform response to restricted interests in children and adolescents with autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *8*(1). https://doi.org/10.1186/s11689-016-9149-6

Gillespie-Smith, K., Doherty-Sneddon, G., Hancock, P. J. B., & Riby, D. M. (2014). That looks familiar: attention allocation to familiar and unfamiliar faces in children with autism

spectrum disorder. *Cognitive Neuropsychiatry*, *19*(6), 554–569. https://doi.org/10.1080/13546805.2014.943365

Goren, C. C., Sarty, M., & Wu, P. Y. K. (1975). Visual Following and Pattern Discrimination of Face-like Stimuli by Newborn Infants. *Pediatrics*, *56*(4), 544–549.

Gotham, K., Risi, S., Dawson, G., Tager-Flusberg, H., Joseph, R., Carter, A., … Hyman, S. L. (2008). A replication of the Autism Diagnostic Observation Schedule (ADOS) revised algorithms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(6), 642–651.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. *Biological Psychiatry*, *51*(1), 59–67. https://doi.org/10.1016/S0006-3223(01)01330-0

Honey, E., Leekam, S., Turner, M., & McConachie, H. (2007). Repetitive behaviour and play in typically developing children and children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(6), 1107–1115.

Johnson, M. H., Dziurawiec, S., Ellis, H., & Morton, J. (1991). Newborns' preferential tracking of face-like stimuli and its subsequent decline. *Cognition*, *40*(1), 1–19.

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature*, *504*(7480), 427–431.

Kaufman, A. S., & Kaufman, N. L. (2004). *Kaufman brief intelligence test*. Wiley Online Library. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/9781118660584.ese1325/summary

Kemner, C., Van Ewijk, L., Van Engeland, H., & Hooge, I. (2008). Brief report: Eye movements during visual search tasks indicate enhanced stimulus discriminability in subjects with PDD. *Journal of Autism and Developmental Disorders*, *38*(3), 553–557.

Kim, J. H., Gunderson, V. M., & Swartz, K. S. (1999). Humans all look alike: Cross-species face recognition in infant pigtailed macaque monkeys. In *biennial meeting of the Society for Research in Child Development, Albuquerque, NM*.

Klin, A., & Jones, W. (2008). Altered face scanning and impaired recognition of biological motion in a 15-month-old infant with autism. *Developmental Science*, *11*(1), 40–46.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, *59*(9), 809–816.

Klin, A., Lin, D. J., Gorrindo, P., Ramsay, G., & Jones, W. (2009). Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature*, *459*(7244), 257–261.

Kohls, G., Chevallier, C., Troiani, V., & Schultz, R. T. (2012). Social 'wanting'dysfunction in autism: neurobiological underpinnings and treatment implications. *Journal of Neurodevelopmental Disorders*, *4*(10), 1–20.

Kuo, M. H., Orsmond, G. I., Coster, W. J., & Cohn, E. S. (2014). Media use among adolescents with autism spectrum disorder. *Autism*, *18*(8), 914–923. https://doi.org/10.1177/1362361313497832

Lam, K. S., & Aman, M. G. (2007). The Repetitive Behavior Scale-Revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(5), 855–866.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism diagnostic observation schedule: ADOS-2*. Western Psychological Services Los Angeles, CA.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685.

MacMullin, J. A., Lunsky, Y., & Weiss, J. A. (2015). Plugged in: Electronics use in youth and young adults with autism spectrum disorder. *Autism*, *20*(1), 1362361314566047. https://doi.org/10.1177/1362361314566047

Mangerud, W. L., Bjerkeset, O., Holmen, T. L., Lydersen, S., & Indredavik, M. S. ebø. (2014). Smoking, alcohol consumption, and drug use among adolescents with psychiatric disorders compared with a population based sample. *Journal of Adolescence*, *37*(7), 1189–1199.

Mazurek, M. O., Shattuck, P. T., Wagner, M., & Cooper, B. P. (2011). Prevalence and Correlates of Screen-Based Media Use Among Youths with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *42*(8), 1757–1767. https://doi.org/10.1007/s10803-011-1413-8

McPartland, J. C., Webb, S. J., Keehn, B., & Dawson, G. (2011). Patterns of visual attention to faces and objects in autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *41*(2), 148–157.

Mottron, L., Dawson, M., Soulieres, I., Hubert, B., & Burack, J. (2006). Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *Journal of Autism and Developmental Disorders*, *36*(1), 27–43.

O'Riordan, M. A. (2004). Superior visual search in adults with autism. *Autism: The International Journal of Research and Practice*, *8*(3), 229–248. https://doi.org/10.1177/1362361304045219

O'Riordan, M. A., Plaisted, K. C., Driver, J., & Baron-Cohen, S. (2001). Superior visual search in autism. *Journal of Experimental Psychology: Human Perception and Performance*, *27*(3), 719.

O'Riordan, M., & Plaisted, K. (2001). Enhanced discrimination in autism. *The Quarterly Journal of Experimental Psychology: Section A*, *54*(4), 961–979.

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual scanning of faces in autism. *Journal of Autism and Developmental Disorders*, *32*(4), 249–261.

Petry, N. M. (2006). Should the scope of addictive behaviors be broadened to include pathological gambling? *Addiction*, *101*(s1), 152–160.

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Archives of General Psychiatry*, *68*(1), 101–109.

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2015). Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated with Increased Symptom Severity. *Biological Psychiatry*. Retrieved from http://www.sciencedirect.com/science/article/pii/S0006322315003108

Plaisted, K., O'Riordan, M., & Baron-Cohen, S. (1998). Enhanced discrimination of novel, highly similar stimuli by adults with autism during a perceptual learning task. *Journal of Child Psychology and Psychiatry*, *39*(5), 765–775.

Santosh, P. J., & Mijovic, A. (2006). Does pervasive developmental disorder protect children and adolescents against drug and alcohol use? *European Child & Adolescent Psychiatry*, *15*(4), 183–188.

Sasson, N. J., Dichter, G. S., & Bodfish, J. W. (2012). Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PloS One*, *7*(8), e42457.

Sasson, N. J., Elison, J. T., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2011). Brief report: Circumscribed attention in young children with autism. *Journal of Autism and Developmental Disorders*, *41*(2), 242–247.

Sasson, N. J., & Touchstone, E. W. (2014). Visual attention to competing social and object images by preschool children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 584–592.

Sasson, N. J., Turner-Brown, L. M., Holtzclaw, T. N., Lam, K. S., & Bodfish, J. W. (2008). Children with autism demonstrate circumscribed attention during passive viewing of complex social and nonsocial picture arrays. *Autism Research*, *1*(1), 31–42.

Schreck, K. A., & Williams, K. (2006). Food preferences and factors influencing food selectivity for children with autism spectrum disorders. *Research in Developmental Disabilities*, *27*(4), 353–363.

Schreck, K. A., Williams, K., & Smith, A. F. (2004). A comparison of eating behaviors between children with and without autism. *Journal of Autism and Developmental Disorders*, *34*(4), 433–438.

Shane-Simpson, C., Brooks, P. J., Obeid, R., Denton, E., & Gillespie-Lynch, K. (2016). Associations between compulsive internet use and the autism spectrum. *Research in Autism Spectrum Disorders*, *23*, 152–165.

Smith, D. G., & Robbins, T. W. (2013). The Neurobiological Underpinnings of Obesity and Binge Eating: A Rationale for Adopting the Food Addiction Model. *Biological Psychiatry*, *73*(9), 804–810. https://doi.org/10.1016/j.biopsych.2012.08.026

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive Behavior Profiles in Asperger Syndrome and High-Functioning Autism. *Journal of Autism & Developmental Disorders*, *35*(2), 145–158.

Sterling, L., Dawson, G., Webb, S., Murias, M., Munson, J., Panagiotides, H., & Aylward, E. (2008). The role of face familiarity in eye tracking of faces by individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *38*(9), 1666–1675.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249.

Turner-Brown, L. M., Lam, K. S. L., Holtzclaw, T. N., Dichter, G. S., & Bodfish, J. W. (2011). Phenomenology and measurement of circumscribed interests in autism spectrum disorders. *Autism*, *15*(4), 437–456. https://doi.org/10.1177/1362361310386507

Valenza, E., Simion, F., Cassia, V. M., & Umiltà, C. (1996). Face preference at birth. *Journal of Experimental Psychology: Human Perception and Performance*, *22*(4), 892–903. https://doi.org/10.1037/0096-1523.22.4.892

Watson, K. K., Miller, S., Hannah, E., Kovac, M., Damiano, C. R., Sabatino-DiCrisco, A., … Dichter, G. S. (2015). Increased reward value of non-social stimuli in children and adolescents with autism. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01026

Young, K. S. (1998). Internet addiction: The emergence of a new clinical disorder. *CyberPsychology & Behavior*, *1*(3), 237–244.

CHAPTER 3

LOW-LEVEL SALIENCE DOES NOT DIFFERENTIALLY INFLUENCE NONSOCIAL VISUAL ATTENTION BETWEEN ADOLESCENTS WITH AUTISM AND TYPICAL DEVELOPMENT

Introduction

Altered attentional (Chawarska, Macari, & Shic, 2013; Kikuchi, Senju, Tojo, Osanai, & Hasegawa, 2009; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Klin, Lin, Gorrindo, Ramsay, & Jones, 2009; Rice, Moriuchi, Jones, & Klin, 2012) and neural responses (Dawson et al., 2005; Kohls et al., 2012) to social information are characteristic of autism spectrum disorder (ASD) and are observed in both children and adults. The social motivation theory of autism proposes that early in life, a lack of motivation for social information contributes to a lack of attentional orienting, and therefore dearth of social experiences, which ultimately contribute to deficient development of socio-communicative behaviors (Dawson, 1991; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Numerous paradigms have been developed to measure social motivation and add evidence to support this hypothesis. One such paradigm is that of preferential viewing, which quantifies visual attention to images in paired arrays. In ASD, these arrays are most often comprised of social versus nonsocial information. Previous studies have demonstrated increased attention to nonsocial information, when compared to social information, in individuals with ASD (Pierce et al., 2015; Pierce, Conant, Hazin, Stoner, & Desmond, 2011).

A line of research originating in our lab suggests that the content of nonsocial stimuli may be particularly important in understanding this attentional bias. Previous studies have found that increased nonsocial attention (paired with decreased social attention) is enhanced when nonsocial stimuli are related to items associated with circumscribed interests (Elison, Sasson, Turner-Brown, Dichter, & Bodfish, 2012; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011; Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008; Sasson & Touchstone, 2014), a behavioral phenomenon that is included in the diagnostic criteria for ASD. Data presented in a previous study (Study 1) demonstrated a context-dependent bias toward nonsocial information in ASD, such that these individuals were slower to orient to social information than typically developing peers, only in the presence of CI-related images. These data suggest that in ASD, certain types of information may compete with and diminish attention to and engagement with social information. It is unclear, however, what factors or mechanisms may be driving this pattern of nonsocial attentional preference. Here, I consider two potential mechanisms for attentional bias in ASD: 1) Attention is driven by low-level features of the stimulus in a bottom-up manner, or 2) Attention is driven by motivation mechanisms in a top-down manner.

The possibility that visual attention is linked to a bottom-up attentional drive is consistent with the Enhanced Perceptual Functioning (EPF) Theory, which postulates that individuals with ASD have enhanced low-level sensory processing abilities (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006). The EPF theory is supported by studies that demonstrate enhanced performance on visual search tasks (Kaldy, Kraper, Carter, & Blaser, 2011; M. A. O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; M. O'Riordan & Plaisted, 2001; K. Plaisted, O'Riordan, & Baron-Cohen, 1998; Kate Plaisted, O'Riordan, & Baron-Cohen, 1998), the Embedded Figures

Task (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983), and detection of orientation in first-order gratings (Bertone, Mottron, Jelenic, & Faubert, 2005) in individuals with ASD, compared to typically developing (TD) peers. Individuals with ASD also demonstrate greater sensitivity to high spatial frequency gratings (Kéïta, Guy, Berthiaume, Mottron, & Bertone, 2014) and display a greater preference for processing local information over than global information (Koldewyn, Jiang, Weigelt, & Kanwisher, 2013; Mottron, Burack, Iarocci, Belleville, & Enns, 2003; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015), relative to individuals with TD. Translated into the natural environment, a bias toward low-level stimulus processing may manifest as increased visual preference for (and, likely, engagement with) objects with visually salient features. Therefore, one hypothesis to explain the previously described enhanced visual attention to CI-related information in preferential viewing arrays is that these images are more visually salient (e.g., more colorful, brighter, or containing sharper lines) than the images with which they are paired.

Top-down attentional drive is consistent with findings of abnormal reward processing in individuals with ASD. Behavioral (Sasson, Dichter, & Bodfish, 2012; Watson et al., 2015) and eye-tracking studies (Elison et al., 2012; Sasson et al., 2011, 2008; Sasson & Touchstone, 2014) demonstrate that individuals with ASD have enhanced non-social motivation relative to TD individuals when the non-social stimuli are related to CIs. Additionally, neuroimaging studies have shown that individuals with ASD and individuals with TD have comparable neural responses in regions associated with reward processing (Dichter, Felder, et al., 2012; Foss-Feig et al., 2016), but show reduced activation when viewing social stimuli (Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Kohls et al., 2012) and non-social stimuli that are not

related to their interests (Cascio et al., 2014; Dichter, Felder, et al., 2012). Therefore, an alternative hypothesis to explain enhanced visual attention to CI-related information in ASD is that these images are more motivating than the social or non-CI-related objects with which they are paired, regardless of low-level stimulus properties.

The purpose of this study was to serve as a set of experimental control analyses for Study 1, which demonstrated quicker orienting to and enhanced visual attention to CI-related stimuli, in adolescents with ASD, using a preferential viewing paradigm. This study tested the hypothesis that increased visual preference for CI-related stimuli is related to the low-level stimulus properties of those images. Gaze data from Study 1 was compared to quantified aspects of low-level stimulus salience to determine if the visual features of an image were related to the specific patterns of visual attention allocated to that image, and if this relationship differed between diagnostic group (ASD vs. TD).

Methods

Participants

Participants included 48 adolescents with ASD (mean age = 167.39 months, range = 116-218 months) and 38 TD adolescents (mean age = 165.83 months, range = 111-227 months. All participants met the following general inclusion criteria: age between 9 and 18 years, intelligence quotient (IQ) above 70, absence of a confounding medical condition such as seizure disorder, acute medical condition, genetic condition, or uncorrected visual impairment. Refer to Table 2.1 for participant demographics.

Participants with ASD were recruited through an autism research registry in conjunction with regional clinics for the assessment and treatment of children and adults with ASD. Inclusion in the registry required a Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of autism from a licensed clinician experienced in the assessment and diagnosis of autism. Diagnosis was based on parent interview and clinician observation using one or more of the following standardized diagnostic assessments for ASD: Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), Social Communication Questionnaire (SCQ; Rutter et al., 2003), and Autism Diagnostic Observation Schedule (ADOS; Rutter et al., 2002). In addition to referral from the registry, all ASD participants were evaluated by trained research personnel using the ADOS, the Social Responsiveness Scale (SRS; Constantino & Gruber, 2002) to examine current severity of ASD symptoms, and the Kaufman Brief Intelligence Test, Second Edition (KBIT-2; Kaufman & Kaufman, 2004) to assess general cognitive ability.

TD participants were recruited via an email sent to university faculty and staff. They were excluded if they had a history of psychiatric or developmental disorder, if they were currently taking psychotropic medication, if an immediate family member had an ASD diagnosis, or if they scored above the ASD cutoff on the SRS. TD participants were matched to ASD participants on chronological age and gender.

One TD participant was excluded for scoring in the ASD range on the SRS. The groups did not differ significantly on nonverbal IQ, $t(62) = 1.60$, $p = .116$. Independent samples t-tests were conducted to assess between-groups differences on each of the psychometric measures and the relevant subscales. As expected, ASD participants scored significantly more severely than TD

participants on measures of social-communication and repetitive behavior. Refer to Table 1.1 for group means and group comparisons on these measures.

Stimuli and Task

Preferential Viewing Task

The preferential viewing task is comprised of 20 static, high-quality color image sets. Each set contains a pair of images: one social (face) image and one object image. The 20 social images were obtained with permission from the MacArthur Foundation Research Network on Early Experience and Brain Development (Tottenham et al., 2009).

Identities of the faces do not repeat, are matched on affect (happy), are divided evenly between males and females, and consist of Caucasian, African-American, and Asian-American individuals. Half of the 20 object stimuli were selected to represent items that are commonly associated with CIs in ASD (e.g., trains, video game consoles, and blocks; South et al., 2005). Our lab has previously validated the reward value of these stimuli for individuals with ASD using standardized valence and arousal ratings (Sasson et al., 2012). ASD participants rated these stimuli as being significantly higher in valence than the control object stimuli. We therefore refer to the CI-related object stimuli as "high autism interest" (HAI) items. The remaining objects are not related to CIs in ASD (e.g., clothing, furniture, and plants), and our lab has demonstrated that participants with ASD rate these images as being significantly lower in valence (Sasson et al., 2012). We refer to these stimuli as "low autism interest" (LAI) items. Two arrays were excluded due to lack of consistency across participant presentation. This resulted in the inclusion of 9 "SOC+HAI" and 9 "SOC+LAI" arrays.

Each image measured approximately 8 x 10 cm, and images in each pair were approximately 12 cm apart. Areas of interest were drawn around each image such that each image in the set was contained in an equivalent area (~20% of the viewing area). Positioning of stimuli (left or right) in each category (face, HAI, LAI) was counterbalanced across pairs.

Eye-tracking

Participants were tested in a research laboratory on the university campus. Participants were seated approximately 60 cm in front of a 17-inch monitor with 1,024 horizontal x 768 vertical resolution and viewed stimuli subtending a visual angle of 16.1°**.** Eye movements were recorded using a Tobii 1750 eye tracker (Tobii Technology, Stockholm, Sweden). This system uses infrared light to generate reflection from the corneas of the eyes and monitors the reflections relative to the position of the eyes. The system has a sampling rate of 60 Hz. The eye-tracking device is mounted to the bottom of the computer monitor and does not interfere with data collection. The system accommodates head movements within a cubic space of 30 x 15 x 20 cm centered at a distance of 60 cm, allowing participants to view the screen in a naturalistic manner. Prior to task administration, participants completed a 5-point calibration procedure, which was repeated until calibration was sufficient for all 5 points. Prior to the task, participants were told to view the stimulus sets however they wanted. Stimulus sets were displayed individually for 5 seconds each. Prior to each stimulus set presentation, an inter-stimulus slide (black with a white fixation cross) appeared for 5 seconds to reorient attention to the center of the screen.

Saliency mapping

The Saliency Toolbox (Itti & Koch, 2001) for MatLab (Mathworks, Inc., Natick, Massachusetts) is a program that identifies and quantifies the most conspicuous (i.e. most likely to capture bottom-up attention) regions of an image. Calculations within the program are based on visual processing within the primate visual system and serve as a computational model of bottom-up visual attention. The toolbox converts qualitative visual features of the image into quantitative "feature maps." These spatially conserved representations of the image denote the regions of the image that are most conspicuous based on each specific visual feature. Values from these three feature maps (color, intensity, orientation) are summed to generate an overall saliency map, which identifies regions of the image that have the greatest *overall* conspicuity (see Figure 3.1).

Feature and saliency maps were generated using the Saliency Toolbox for all images in the above described Paired Preference task. Four saliency scores were generated for each image: color, intensity, orientation, and a composite score (linear sum of the three features; see Figure 3.2). These scores were generated by summing across conspicuity values for each feature map.

Analysis of task performance

The paired preference task requires that participants look at the trial for a sufficient amount of time to allow them to observe both images in the set. Therefore, criteria were established for excluding participants based on insufficient total look time per set. Participants who spent less than 2.5 seconds (half of the time the set was presented) viewing more than 10 of the 18 sets were excluded from the analyses. Based on these criteria, 15 participants with ASD and 7 TD participants were excluded. The excluded individuals did not differ from the included individuals

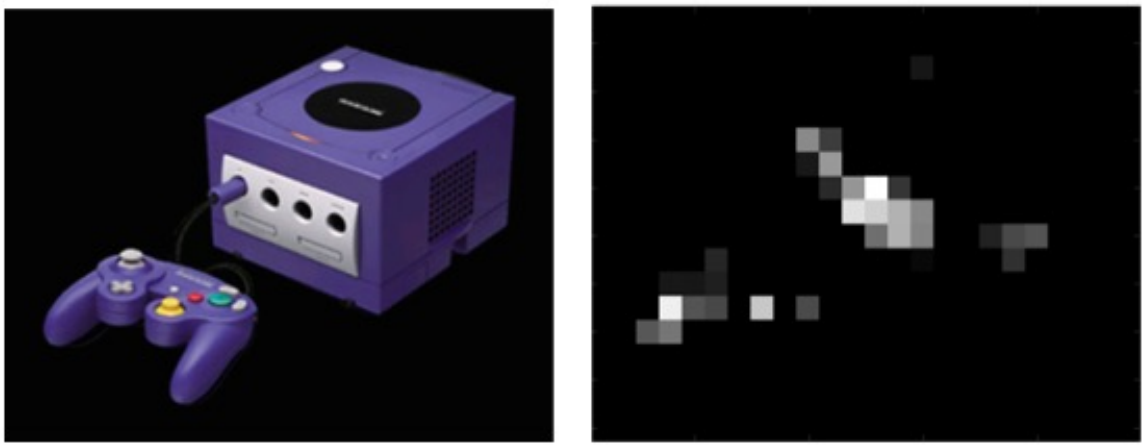

Figure 3.1 **Sample stimulus and saliency map**. An example of an HAI image (left) and its corresponding saliency map (right) for the combined low-level features. *HAI*, high autism interest

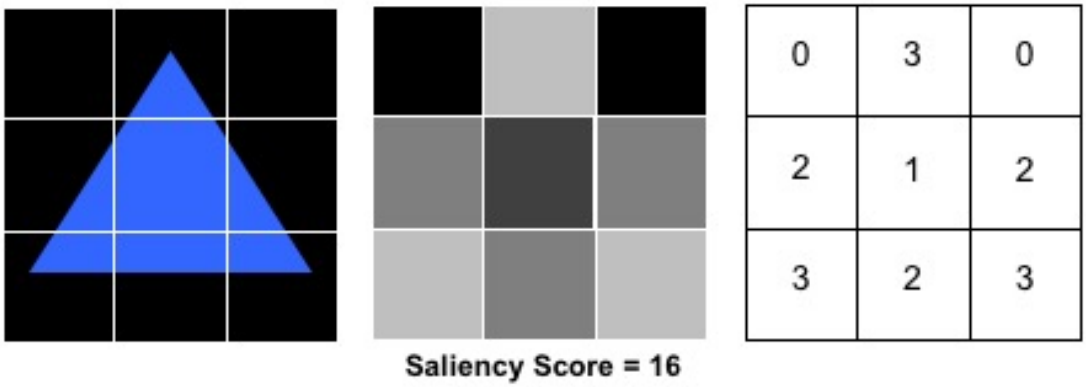

Figure 3.2 **Sample calculation of saliency scores**. A simplified depiction of how saliency scores were derived. The first panel represents the image. The second panel represents the saliency map for the image. The third panel is the numerical matrix of saliency values that the Saliency Toolbox uses to generate the saliency map, and the saliency scores were generated by summing the cells of the numerical matrix for the image, giving a saliency score of 16 for this example.

on age ($t(84) = 1.24$, $p = .217$) or nonverbal IQ ($t(82) = .507$, $p = .613$); however, the excluded group had a significantly greater proportion of females than the included group.

Statistical analysis

Two paths of analysis were utilized in this study: 1) To determine whether low-level visual saliency was locally associated with participant gaze patterns. 2) To determine whether low-level visual saliency was globally associated with participant gaze patterns. Here, I assessed the relationship between saliency scores and total viewing time to each image.

Local analysis rationale

For this approach, the relationship was assessed between saliency scores and initial fixation to each image. Studies of visual attention in the typical population have demonstrated that low-level visual features are more effective at predicting patterns of gaze shortly after stimulus presentation (Carmi & Itti, 2006; Parkhurst, Law, & Niebur, 2002). Therefore, analysis of initial fixations may reflect the largest overall effect of saliency. Two sets of analyses were performed. First, correlations were assessed between the latency to first fixate on an image (prioritization) and individual saliency scores (color, luminance, orientation, composite) for each image. Second, the most visually salient region in each image was identified per the image composite saliency score. Each image was then coded for the percentage of participants for which this region was the location of his or her first fixation. Chi-square analyses were used to assess diagnostic (ASD vs. TD) group differences.

Global analysis rationale

Global analyses were performed to assess the relationship between saliency and two indices of overall attention. Preference was calculated as the proportion of total look time spent on an image, relative to time spent on the opposite image in the array. Therefore, this variable allows for analysis of low-level saliency effects in the context of social vs. nonsocial image competition. Average Fixation Duration was calculated as the average length of fixation on a given image. This variable is a commonly used in analyses of gaze patterns and, importantly, is independent of the competition between social and nonsocial attention. Correlations between this variable and a given saliency score would, therefore, indicate an effect of low-level salience independent of cognitive bias relating to stimuli in the set.

Results

Analysis of gaze dynamics

Prioritization refers to the latency to make the first fixation to an image. A 2x2 (Group: ASD, TD; Array: SOC+LAI, SOC+HAI) repeated measures analysis of variance was conducted for prioritization to social images. A group x array interaction was at trend-level significance ($F(2, 62) = 3.58$, $p = .063$). There was a main effect of array ($F(1, 62) = 5.23$, $p = .026$), and a trend-level main effect of group ($F(1, 62) = 3.44$, $p = .068$). Post-hoc paired-samples t-tests show that for the ASD group only, latency to the social image is significantly slower when social images are paired with HAI images, compared to LAI images ($t(32) = -2.53$, $p = .02$).

Preference refers to the proportion of time spent viewing an image, accounting for the total time spent on the stimulus. A 2x2 (Group: ASD, TD; Array: SOC+LAI, SOC+HAI) repeated

measures analysis of variance was conducted for preference for object images. There was no group x array interaction ($p = .164$). There was a main effect of array ($F(1, 62) = 34.90$, $p < .0001$). There was a main effect of group ($F(1, 62) = 7.95$, $p < .01$). Main effect results indicate both groups showed greater preference for objects in SOC + HAI arrays, compared to SOC + LAI arrays. Additionally, the ASD group showed greater total fixation time for objects than the TD group in both array types.

Local analyses: Prioritization

Pearson's correlations were used to assess the relationship between prioritization and saliency values. Data were analyzed according to diagnostic group, image type, and saliency component (color, intensity, orientation, and composite). Individual participant data for a given image was excluded if the participant made no fixations to the image. Results are summarized in Table 3.1.

For social images within SOC+LAI arrays, no significant correlations between prioritization and saliency scores were observed for either group. For social images within SOC+HAI arrays, a positive correlation was observed between prioritization and both orientation ($r = .142$, $p = .011$) and composite ($r = .103$, $p = .048$) saliency scores, for TD participants only. No significant correlations were observed for participants with ASD

Table 3.1 *Correlations of Prioritization and Saliency Scores*

		ASD			TD		
Image Type	Saliency Component	r	p	N	r	p	N
Social Paired with LAI	*Color*	0.061	0.179		-0.058	0.173	
	Intensity	0.027	0.343		-0.022	0.359	
	Orientation	0.079	0.117		-0.027	0.332	
	Composite	0.087	0.095	230	-0.016	0.395	264
LAI	*Color*	0.033	0.3		**-0.136***	**0.016**	
	Intensity	-0.024	0.349		-0.047	0.232	
	Orientation	-0.037	0.458		-0.042	0.256	
	Composite	0.038	0.27	260	-0.057	0.186	249
Social Paired with HAI	*Color*	-0.076	0.135		0	0.498	
	Intensity	-0.011	0.438		0.054	0.193	
	Orientation	0.09	0.095		**0.142***	**0.011**	
	Composite	0.049	0.238	211	**0.103***	**0.048**	261
HAI	*Color*	-0.071	0.127		0.071	0.128	
	Intensity	0.051	0.204		-0.072	0.125	
	Orientation	0.07	0.128		-0.012	0.425	
	Composite	0.019	0.38	263	-0.024	0.347	260

N values reflect the number of image-participant comparisons that were included the analyses for the given image type. *, $p < .05$; ASD, Autism Spectrum Disorder; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

For object images within SOC+LAI arrays, a negative correlation was observed between prioritization and color (r = -.136, p = .016) for TD participants. No significant correlations were observed for participants with ASD. For object images within SOC+HAI arrays, no significant correlations were observed between prioritization and saliency scores for either group.

Local analyses: Location

Chi-square tests were used to determine if diagnostic groups differed in the proportion of participants whose first fixation fell within the most visually salient region of an image. Data were analyzed according to image type. No group differences were observed between groups for any image type (SOC+LAI Faces χ^2 = .004, p = .974; SOC+HAI Faces χ^2 = .046, p = .83; SOC+LAI Objects χ^2 = .046, p = .83; SOC+HAI Objects χ^2 = 1.14, p = .25).

Global analyses: Preference

Pearson's correlations were used to assess the relationship between preference and saliency values. Data were analyzed according to diagnostic group, image type, and saliency component (color, intensity, orientation, and composite). Individual participant data for a given image was excluded if the participant made no fixations to the image. Results are summarized in Table 3.2.

For social images in SOC+LAI arrays, no significant correlations were observed between preference and saliency scores for either group. For social images in SOC+HAI arrays, a significant correlation was observed between preference and orientation (r = .111, p = .032) for TD participants. No significant correlations were observed for participants with ASD.

Table 3.2 *Correlations of Preference and Saliency Scores*

		ASD			TD		
Image Type	Saliency Component	r	p	N	r	p	N
Social Paired with LAI	*Color*	-0.077	0.102		0.078	0.098	
	Intensity	0.094	0.059		0.039	0.262	
	Orientation	0.049	0.211		0.048	0.215	
	Composite	0.027	0.326	275	0.093	0.063	274
LAI	*Color*	**-0.133***	**0.014**		-0.091	0.067	
	Intensity	0.02	0.369		0.033	0.291	
	Orientation	0.036	0.274		0.067	0.135	
	Composite	-0.075	0.106	275	-0.025	0.341	274
Social Paired with HAI	*Color*	0.012	0.42		-0.058	0.166	
	Intensity	-0.031	0.302		-0.046	0.222	
	Orientation	-0.005	0.466		**0.111***	**0.032**	
	Composite	-0.073	0.112	276	-0.069	0.124	281
HAI	*Color*	-0.054	0.185		**-0.124***	**0.019**	
	Intensity	0.042	0.244		**0.234***	**0**	
	Orientation	0.036	0.277		**0.230***	**0**	
	Composite	**0.124***	**0.02**	277	**0.213***	**0**	279

N values reflect the number of image-participant comparisons that were included the analyses for the given image type. *, $p < .05$; ASD, Autism Spectrum Disorder; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

For object images in SOC+LAI arrays, a significant correlation was observed between preference and color (r = -.133, p = .014) for participants with ASD. No significant correlations were observed for participants with TD. For object images in HAI arrays, a significant correlation was observed between preference and composite scores for both TD (r = .213, p < .001) and ASD (r = .124, p = .02) participants. Further, individual component scores were significantly correlated with preference (color, r = .124, p = .019; intensity, r = .234, p < .001; orientation, r = .230, p < .001) for TD participants. Individual component scores were not significantly correlated with preference for participants with ASD. Figure 3.3 depicts correlations between preference and composite saliency scores for each group.

Global analyses: Average fixation duration

Pearson's correlations were used to assess the relationship between average fixation duration and saliency values. Data were analyzed according to diagnostic group, image type, and saliency component (color, intensity, orientation, and composite). Individual participant data for a given image was excluded if the participant made no fixations to the image. Results are summarized in Table 3.3.

For social images in SOC+LAI arrays, a significant correlation was observed between average fixation duration and composite saliency (r = .233, p < .001), as well as all component scores (Color: r = .180, p = .002; Intensity: r = .180, p = .002; Orientation: r = .130, p = .017), for TD participants. No significant correlations were observed for participants with ASD. For social images in SOC+HAI arrays, no significant correlations were observed for either group.

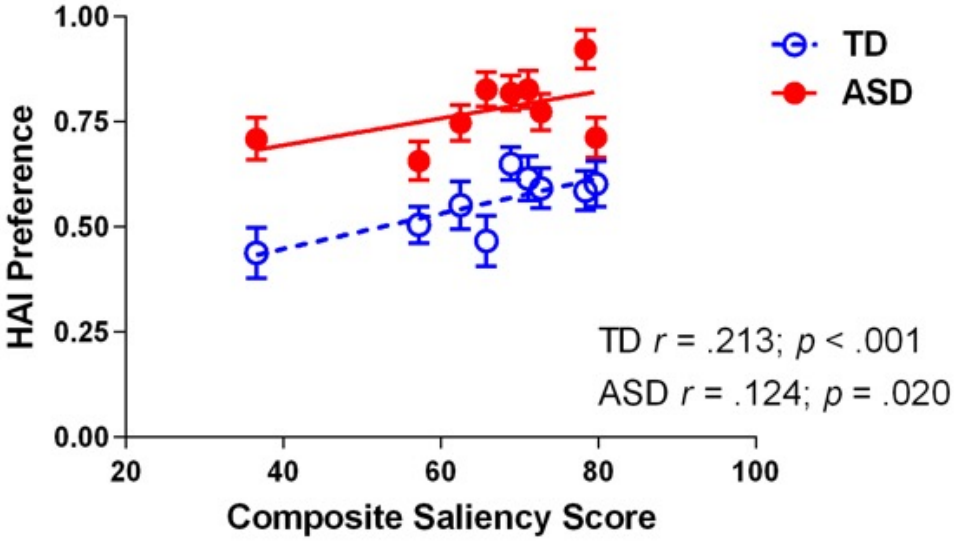

Figure 3.3 **Correlation between HAI preference and composite saliency.** Correlations between composite saliency for HAI images and the gaze variable, Preference, in individuals with ASD (solid red) and TD (open blue). Error bars represent standard error of the mean. *ASD,* Autism Spectrum Disorder; *TD*, typically developing; *HAI*, high autism interest.

Table 3.3 *Correlations of Average Fixation Duration and Saliency Scores*

		ASD			TD		
Image Type	Saliency Component	r	p	N	r	p	N
Social Paired with LAI	*Color*	-0.017	0.398		**0.180***	**0.002**	
	Intensity	0.054	0.208		**0.180***	**0.002**	
	Orientation	-0.016	0.403		**0.130***	**0.017**	
	Composite	0.034	0.306	229	**0.233***	**0**	264
LAI	*Color*	0.065	0.148		0.024	0.355	
	Intensity	-0.004	0.475		0.035	0.291	
	Orientation	-0.022	0.359		-0.018	0.389	
	Composite	0.02	0.373	260	0.024	0.354	251
Social Paired with HAI	*Color*	-0.014	0.418		0.033	0.3	
	Intensity	0.035	0.308		-0.038	0.269	
	Orientation	-0.024	0.363		-0.015	0.405	
	Composite	-0.077	0.132	212	-0.014	0.412	261
HAI	*Color*	0.042	0.251		-0.085	0.085	
	Intensity	0.045	0.235		**0.147***	**0.009**	
	Orientation	0.07	0.129		0.08	0.1	
	Composite	0.055	0.185	263	0.093	0.068	260

For object images in SOC+LAI arrays, no significant correlations were observed for either group. For object images in SOC+HAI arrays, a significant correlation was observed between average fixation duration and intensity (r = .147, p = .009) for individuals with TD. No significant correlations were observed for participants with ASD.

Strength of effect

Fisher r-to-z transformation was used to compare correlations between groups. Group comparisons were made if a significant correlation was observed between a given gaze parameter and saliency score in both groups. This resulted in transformation of correlation coefficients that corresponded to the relationship between preference and composite salience values. There were no significant between-group differences for the correlation between preference and the composite score for HAI images (z = 1.07, p = .142).

Discussion

The purpose of this study was to examine the relationship between patterns of visual attention and low-level visual salience, in the context of a preferential viewing task. These analyses were pursued for both local (considering only the initial fixation and / or the most salient region of the image) and global (considering the whole image image and / or entire duration of viewing) aspects of attention, to test the hypothesis that nonsocial attentional bias in ASD is related to low-level visual features of the image. Local analyses revealed no relationship between gaze patterns and salience values for either group, for any stimulus category. Global analyses revealed a pattern of increased preference for HAI images with high composite saliency scores, across all participants. The magnitude of this effect did not differ between diagnostic group.

Taken together, found minimal effects of composite salience were found on social or object viewing in individuals with ASD. Even where effects were present, these did not differ in magnitude from TD peers. These effects are consistent with at least one other study that examined low-level saliency in post-hoc analyses, rather than through planned study design. Fletcher-Watson et al. (2009) used saliency mapping in an attempt to draw out more nuanced differences between TD and ASD groups while viewing paired social versus nonsocial scenes, as global attentional patterns had not differed. Analyses revealed orientation as the best predictor of gaze patterns (a composite score was not included in the analyses), but no aspect of low-level saliency predicted visual attention differently between groups. The results of the current study are further consistent with studies specifically designed to address the relationship between gaze patterns and low-level visual features. For example, Neumann et al. (2006) visually manipulated the low-level salience properties of faces to test whether innate saliency differences in facial features drive the altered facial scanning patterns that are often observed in ASD. However, results indicated that visual attention to faces of varying affect was less associated with low-level visual properties in adults with ASD than TD adults. Finally, Freeth et al. (2011) found no group differences in the location of initial fixations to regions of social scenes that were more salient versus less salient, again suggesting a similar contribution of low-level visual salience to patterns of visual attention between ASD and TD.

This study did not find a relationship between the location of the first fixation and the visual salience of the image, for either group. Therefore, it can be can concluded that initial orienting was likely due to the content of the image, rather than its physical characteristics. This is

particularly important for the interpretability of Study 1, which found that social orienting was delayed in ASD, compared to TD, only for social images that were paired with CI-related images. Therefore, the difference in low-level salience between LAI and HAI is critical in understanding the nature of this differential pattern of attention. Results from this study serve as a "control" experiment to indicate that this ASD-specific pattern was not a factor of salience-driven differences.

Results from Study 1 demonstrated a significant increase in preference for CI-related images in individuals with ASD, compared to TD. This study did find a modest, but significant, relationship between global attention (preference) and the salience of CI-related images in both individuals with ASD and those with TD. However, Fisher's r-to-z transformation revealed no difference in the strength of this correlation, suggesting that, in the context of this task, individuals with ASD are no more influenced by the visual salience of CI-related items than TD peers. This experimental control allows us to make the interpretation that individuals with ASD likely allocated more attention to CI-related stimuli due to top-down attentional modulation, rather than being driven by mechanisms of bottom-up attention. This interpretation is consistent with findings from studies of reward processing in ASD which have demonstrated that individuals with ASD have enhanced motivation to view stimuli related to their specific interests (Watson et al., 2015), enhanced activation in components of the reward circuit (e.g., insula and anterior cingulate cortex) when viewing stimuli related to their interests (Cascio et al., 2014), and reduced reward circuitry activation (e.g., nucleus accumbens, anterior cingulate cortex, and amygdala) for social stimuli and non-social stimuli that are unrelated to their interests, compared to TD peers (Dichter, Richey, et al., 2012; Kohls et al., 2012).

Mechanisms of experience-dependent development may be relevant in understanding the role of low-level salience on visual attention. For example, a recent study by Amso et al. (2014) demonstrated a greater effect of low-level visual features on initial fixations to social scenes for children with ASD, compared to children with TD. Therefore, bottom-up attention may exert greater control over patterns of visual attention early in life, compared to during adolescence and adulthood. Further, attention capture rarely happens solely through bottom-up mechanisms. Rather, orienting is facilitated through an interaction of experience and task-relevant cognitive "settings" (Folk, Remington, & Johnston, 1992; Greenaway & Plaisted, 2005). In the case of typical development, this may mean that increased experience with social information leads to an increase in top-down guided orienting toward social information. Conversely, in ASD, enhanced motivation and attention to nonsocial information in the environment may lead to increased experience with specific types of nonsocial information. If this occurs early in development, it may lead to these individuals achieving a level of "expertise" in their area of interest. Expertise on the subject of an image has been found to moderate the effect of low-level features on gaze patterns during eye-tracking tasks (Brunye et al., 2014; Humphrey & Underwood, 2009). For example, in a study of college-level engineering and American history students, low-level visual features influenced gaze patterns less when the students viewed images pertaining to their area of study (engineering-related images or images of Civil War relics, respectively) compared to when the images were unrelated to their area of study (Brunye et al., 2014). Further, gaze patterns of breast pathology specialists were more influenced by diagnostically relevant regions of breast tissue images and less influenced by low-level visual features than for medical personnel with less breast pathology experience (Humphrey & Underwood, 2009). "Expertise" in a CI may

allow individuals with ASD to override the salience of low-level image features and instead direct their gaze to semantically relevant features. A recent study found that individuals with ASD have increased activation relative to TD individuals in the fusiform gyrus, a brain region associated with face discrimination and visual expertise, when participants viewed stimuli relating to their specific interest, supporting the notion that individuals with ASD have unique expertise regarding their CIs (Foss-Feig et al., 2016).

A key limitation of this study is that low-level features of stimuli were not systematically manipulated, as these analyses were conducted post-hoc, rather than *a priori* to study design. Rather, saliency was quantified for existing stimuli using the Saliency Toolbox. This may have limited the within stimulus variability or contributed to a lack of representation of the full range of salience combinations or possibilities (e.g., high orientation score + low color score). This may be especially relevant for luminance saliency scores, as our initial task controlled for cross-category luminance values. The relationship between low-level visual features and gaze dynamics in ASD should be explored further with studies that manipulate aspects of stimulus salience (i.e. systematically filtering out different colors, adjusting the luminance, or sharpening or softening the focus).

The results from the current study provide a level of control that supports conclusions drawn from Study 1. Low-level stimulus saliency does not contribute to attentional orienting toward faces or objects, in individuals with TD or ASD. Therefore, differences in how quickly these individuals orient to these objects is likely due to the content of the image, rather than its physical characteristics. Further, individuals with ASD and TD are not differentially influenced

by the low-level salience properties of CI-related images. This indicates that overall increased attention to these images, as demonstrated in ASD, can be attributed to top-down mechanisms of attention. Specifically, this attention may reflect increased motivation for and expertise for such items, both which may contribute to attention being directed based on stimulus content.

REFERENCES

Amso, D., Haas, S., Tenenbaum, E., Markant, J., & Sheinkopf, S. J. (2014). Bottom-up attention orienting in young children with autism. *Journal of Autism and Developmental Disorders*, *44*(3), 664–673.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain*, *128*(10), 2430–2441.

Brunye, T. T., Carney, P. A., Allison, K. H., Shapiro, L. G., Weaver, D. L., & Elmore, J. G. (2014). Eye movements as an index of pathologist visual expertise: a pilot study. *PloS One*, *9*(8), e103447.

Carmi, R., & Itti, L. (2006). Visual causes versus correlates of attentional selection in dynamic scenes. *Vision Research*, *46*(26), 4333–4345.

Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P., … Cao, A. (2014). Affective neural response to restricted interests in autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*(2), 162–171.

Chawarska, K., Macari, S., & Shic, F. (2013). Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. *Biological Psychiatry*, *74*(3), 195–203.

Dawson, G. (1991). VIII A Psychobiological Perspective on the Early Socio-emotional Development of Children with Autism. *Models and Integrations*, *3*, 207.

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders*, *28*(6), 479–485.

Dawson, G., Webb, S. J., Wijsman, E., Schellenberg, G., Estes, A., Munson, J., & Faja, S. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology*, *17*(03), 679–697.

Dichter, G. S., Felder, J. N., Green, S. R., Rittenberg, A. M., Sasson, N. J., & Bodfish, J. W. (2012). Reward circuitry function in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *7*(2), 160–172.

Dichter, G. S., Richey, J. A., Rittenberg, A. M., Sabatino, A., & Bodfish, J. W. (2012). Reward circuitry function in autism during face anticipation and outcomes. *Journal of Autism and Developmental Disorders*, *42*(2), 147–160.

Elison, J. T., Sasson, N. J., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2012). Age trends in visual exploration of social and nonsocial information in children with autism. *Research in Autism Spectrum Disorders*, *6*(2), 842–851.

Fletcher-Watson, S., Leekam, S. R., Benson, V., Frank, M. C., & Findlay, J. M. (2009). Eye-movements reveal attention to social information in autism spectrum disorder. *Neuropsychologia*, *47*(1), 248–257.

Folk, C. L., Remington, R. W., & Johnston, J. C. (1992). Involuntary covert orienting is contingent on attentional control settings. *Journal of Experimental Psychology Human Perception and Performance*, *18*, 1030–1030.

Foss-Feig, J. H., McGugin, R. W., Gauthier, I., Mash, L. E., Ventola, P., & Cascio, C. J. (2016). A functional neuroimaging study of fusiform response to restricted interests in children and adolescents with autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *8*(1). https://doi.org/10.1186/s11689-016-9149-6

Freeth, M., Foulsham, T., & Chapman, P. (2011). The influence of visual saliency on fixation patterns in individuals with Autism Spectrum Disorders. *Neuropsychologia*, *49*(1), 156–160.

Greenaway, R., & Plaisted, K. (2005). Top-down attentional modulation in autistic spectrum disorders is stimulus-specific. *Psychological Science*, *16*(12), 987–994.

Humphrey, K., & Underwood, G. (2009). Domain knowledge moderates the influence of visual saliency in scene recognition. *British Journal of Psychology*, *100*(2), 377–398.

Itti, L., & Koch, C. (2001). Computational modelling of visual attention. *Nature Reviews Neuroscience*, *2*(3), 194–203.

Jolliffe, T., & Baron-Cohen, S. (1997). Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? *Journal of Child Psychology and Psychiatry*, *38*(5), 527–534.

Kaldy, Z., Kraper, C., Carter, A. S., & Blaser, E. (2011). Toddlers with autism spectrum disorder are more successful at visual search than typically developing toddlers. *Developmental Science*, *14*(5), 980–988.

Kéïta, L., Guy, J., Berthiaume, C., Mottron, L., & Bertone, A. (2014). An early origin for detailed perception in Autism Spectrum Disorder: biased sensitivity for high-spatial frequency information. *Scientific Reports*, *4*, 5475.

Kikuchi, Y., Senju, A., Tojo, Y., Osanai, H., & Hasegawa, T. (2009). Faces do not capture special attention in children with autism spectrum disorder: A change blindness study. *Child Development*, *80*(5), 1421–1433.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, *59*(9), 809–816.

Klin, A., Lin, D. J., Gorrindo, P., Ramsay, G., & Jones, W. (2009). Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature*, *459*(7244), 257–261.

Kohls, G., Schulte-Rüther, M., Nehrkorn, B., Müller, K., Fink, G. R., Kamp-Becker, I., … Konrad, K. (2012). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, nss033.

Koldewyn, K., Jiang, Y. V., Weigelt, S., & Kanwisher, N. (2013). Global/local processing in autism: Not a disability, but a disinclination. *Journal of Autism and Developmental Disorders*, *43*(10), 2329–2340.

Mottron, L., Burack, J. A., Iarocci, G., Belleville, S., & Enns, J. T. (2003). Locally oriented perception with intact global processing among adolescents with high-functioning autism: evidence from multiple paradigms. *Journal of Child Psychology and Psychiatry*, *44*(6), 904–913.

Mottron, L., Dawson, M., Soulieres, I., Hubert, B., & Burack, J. (2006). Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *Journal of Autism and Developmental Disorders*, *36*(1), 27–43.

Neumann, D., Spezio, M. L., Piven, J., & Adolphs, R. (2006). Looking you in the mouth: abnormal gaze in autism resulting from impaired top-down modulation of visual attention. *Social Cognitive and Affective Neuroscience*, *1*(3), 194–202.

O'Riordan, M. A., Plaisted, K. C., Driver, J., & Baron-Cohen, S. (2001). Superior visual search in autism. *Journal of Experimental Psychology: Human Perception and Performance*, *27*(3), 719.

O'Riordan, M., & Plaisted, K. (2001). Enhanced discrimination in autism. *The Quarterly Journal of Experimental Psychology: Section A*, *54*(4), 961–979.

Parkhurst, D., Law, K., & Niebur, E. (2002). Modeling the role of salience in the allocation of overt visual attention. *Vision Research*, *42*(1), 107–123.

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Archives of General Psychiatry*, *68*(1), 101–109.

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2015). Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated with Increased Symptom Severity. *Biological Psychiatry*. Retrieved from http://www.sciencedirect.com/science/article/pii/S0006322315003108

Plaisted, K., O'Riordan, M., & Baron-Cohen, S. (1998). Enhanced discrimination of novel, highly similar stimuli by adults with autism during a perceptual learning task. *Journal of Child Psychology and Psychiatry*, *39*(5), 765–775.

Plaisted, K., O'Riordan, M., & Baron-Cohen, S. (1998). Enhanced visual search for a conjunctive target in autism: a research note. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *39*(5), 777–783.

Rice, K., Moriuchi, J. M., Jones, W., & Klin, A. (2012). Parsing heterogeneity in autism spectrum disorders: visual scanning of dynamic social scenes in school-aged children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(3), 238–248.

Sasson, N. J., Dichter, G. S., & Bodfish, J. W. (2012). Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PloS One*, *7*(8), e42457.

Sasson, N. J., Elison, J. T., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2011). Brief report: Circumscribed attention in young children with autism. *Journal of Autism and Developmental Disorders*, *41*(2), 242–247.

Sasson, N. J., & Touchstone, E. W. (2014). Visual attention to competing social and object images by preschool children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 584–592.

Sasson, N. J., Turner-Brown, L. M., Holtzclaw, T. N., Lam, K. S., & Bodfish, J. W. (2008). Children with autism demonstrate circumscribed attention during passive viewing of complex social and nonsocial picture arrays. *Autism Research*, *1*(1), 31–42.

Shah, A., & Frith, U. (1983). An islet of ability in autistic children: A research note. *Journal of Child Psychology and Psychiatry*, *24*(4), 613–620.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249.

Van Eylen, L., Boets, B., Steyaert, J., Wagemans, J., & Noens, I. (2015). Local and global visual processing in autism spectrum disorders: Influence of task and sample characteristics and relation to symptom severity. *Journal of Autism and Developmental Disorders*, 1–23.

Watson, K. K., Miller, S., Hannah, E., Kovac, M., Damiano, C. R., Sabatino-DiCrisco, A., … Dichter, G. S. (2015). Increased reward value of non-social stimuli in children and adolescents with autism. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01026

CHAPTER 4

DEVELOPMENT OF AN EYE-TRACKING BIOMARKER TO MEASURE SOCIAL MOTIVATION IN AUTISM ACROSS THE SPECTRUM OF COGNITIVE ABILITY

Introduction

Varying epidemiologic studies suggest that anywhere from 30-70% of individuals with autism spectrum disorder (ASD) have a degree of co-morbid intellectual disability (ID). Most recently, an estimate from the CDC found that in a large sample of children, nearly half (46%) displayed a clear diagnosis of ASD as well as clinically significant deficits in intellectual and adaptive behavior (Tonnsen et al., 2016). Notably, co-morbid ID is not part of the diagnostic criteria for autism spectrum disorders. Such a pattern of co-occurrence has two primary implications. First, there may be mechanistic commonalities between these two diagnoses, such that risk for ID confers risk for ASD. High prevalence of ID in ASD (ASD+ID) suggests that these two diagnoses share common etiological risk factors. Therefore, research that examines commonalities between individuals with ASD with and without co-occurring ID may be particularly applicable to a research domain criterion (RDoC) approach. Second, ASD with co-occurring ID may account for critical differences in the manifestation and / or severity of ASD symptomology. These individuals may exhibit more frequent stereotyped motor movements and more restricted play (Bryson, Bradley, Thompson, & Wainwright, 2008; Nordin & Gillberg, 1996; Tonnsen et al., 2016), have greater rates of language impairment (i.e. display minimal verbal ability; Ellis Weismer & Kover, 2015; Rose, Trembath, Keen, & Paynter, 2016), and have increased challenging behaviors (Kim, Macari, Koller, & Chawarska, 2016; Papadopoulos et al.,

2012; Rattaz, Michelon, & Baghdadli, 2015) and medical co-morbidities (McElhanon, McCracken, Karpen, & Sharp, 2014). Therefore, research is also needed to understand differences between ASD with and without ID to inform potential variations in approach to screening, treatment, and application of outcome measures.

Despite the potential importance of examining similarities and differences between ASD with and without comorbid ID, very little research to date has been focused on this. An informal overview of ASD studies in PubMed over the last 20 years determined that fewer than 5% of studies included individuals with ASD+ID. A recently published meta-analysis of visual processing research in ASD found that only 20% of these studies included individuals with co-occurring ID (Brown, Chouinard, & Crewther, 2017). Notably, this bias seemed to be largely due to selectively sampling participants within a "normal" IQ range, with most studies reporting average IQs between 95 and 115. It is clear that despite the wide range of cognitive abilities that characterize the ASD population, ASD research in general, and ASD visual processing research in particular, is highly restricted to studies of "high functioning" ASD. It is unlikely that findings from this research can be directly generalized to the subset of the spectrum of individuals with ASD+ID, given the documented phenotypic and potential genetic differences between these two groups.

Based on this information, it seems imperative to extend research in ASD to include more participants with comorbid ID. Closing this this gap in the ASD knowledge base, however, will require the development and application of research tasks and paradigms that are feasible in individuals with ASD+ID or can be adapted for increased feasibility. Only once methods are

developed and employed that permit valid and reliable measurement for persons of varying degrees of cognitive ability will the field be better able to discover the key similarities and differences between ASD and ASD+ID.

The first aim of this study was to assess the feasibility of a previously developed paired preference eye-tracking task (Unruh et al., 2016) to study individuals with ASD and no cognitive impairments for testing individuals with ASD+ID. Unlike some methodologies, eye-tracking may be particularly suited for data collection in this population because it is noninvasive, can often be completed relatively quickly, and can be designed to place minimal task demands on participants (Tager-Flusberg & Kasari, 2013). Previous studies in our lab have used eye-tracking to measure aspects of visual attention in both children and adolescents with ASD and typical development. These studies have shown high levels of feasibility and data quality across participant groups and ages. One such task is a preferential viewing paradigm, which can be used to assess patterns of attentional bias. The logic of this paradigm is that when images are paired, the resulting pattern of visual orientation and attention can give insight into the relative preference or reward value of the two stimulus types. Notably, analogous assays have been used to assess preferential viewing even in early infancy (Fantz, 1964; Goren, Sarty, & Wu, 1975; Johnson, Dziurawiec, Ellis, & Morton, 1991; Valenza, Simion, Cassia, & Umiltà, 1996), suggesting that such a task may be ideal for application across levels of development and / or functional and adaptive ability.

The second aim of the study was to assess whether individuals with ASD + ID show similar patterns of visual attention to their peers with ASD and no co-occurring ID. In a previous study

(Unruh et al., 2016), preferential viewing was used to test the hypothesis that the presence of a specific type of nonsocial stimuli (images depicting commonly occurring items of circumscribed interest in ASD) biases attention in adolescents with ASD and interferes with attention to social stimuli. Results of this study demonstrated that individuals with ASD and no co-occurring ID show decreased preference for social images and are slow to orient to to this information, particularly when in the presence of a highly salient competing image. In the current study, I hypothesized that individuals with ASD+ID would show similar patterns of results, with potentially exaggerated delays in orienting.

Methods

Participants

Three groups of adolescents participated in this study. The first group was comprised of individuals with ASD and no comorbid intellectual disability (ASD; N = 47; mean age = 13.9 years). The second group was comprised of individuals with ASD and co-occurring intellectual disability (ASD+ID; N = 11; mean age = 11.9 years). A group of individuals with typical development comprised the third group (TD; N = 39; mean age = 13.8 years). All participants met the following general inclusion criteria: age between 9 and 18 years; absence of seizure disorder, acute medical, or genetic condition; and absence of any visual impairment uncorrectable with eyeglasses. Importantly, individuals in the ASD group were specifically recruited for either an IQ that was at or above 90 or below 70. In this way, two divergent groups of participants with ASD were established, either with or without co-morbid ID, rather than including a continuous range of participant IQs. See Table 4.1 for participant demographics.

Participants with ASD were recruited through an autism research registry in conjunction with regional assessment and treatment clinical service programs for persons with ASD. Inclusion of the registry required a previous Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of ASD made by a licensed clinician experienced in the assessment and diagnosis of autism, and based on parent interview and direct observation for the completion standardized autism diagnostic assessment instruments (Autism Diagnostic Interview-Revised; ADI-R), Autism Diagnostic Observation Schedule; ADOS). Following referral from the registry, all ASD participants were evaluated by trained study personnel using (a) the ADI-R (Lord, Rutter, & Le Couteur, 1994) to examine lifetime criteria for ASD, (b) the ADOS (Lord et al., 2012), (c) the Social Responsiveness Scale (SRS) (Constantino & Gruber, 2002) to examine the current severity of autism symptoms, and (d) the Kaufman Brief Intelligence Test, Second Edition (KBIT-2) (Kaufman & Kaufman, 2004) to examine general cognitive ability.

TD children were recruited via an email sent university faculty and staff. TD children were excluded if they had a history of psychiatric or developmental disorder, if they were currently taking psychotropic medication, if an immediate family member had an ASD diagnosis, or if they received a score above the ASD cutoff on the SRS. These adolescents were chosen to be matched on gender and chronological age, compared to the ASD group. Groups were matched on gender because previous studies indicate interest in social stimuli and CI-related stimuli can vary between males and females (Sasson, Dichter, & Bodfish, 2012).

Table 4.1 *Demographics and Participant Characterization for Study 3*

Characteristic	ASD (N = 47)	ASD+ID (N = 11)	TYP (N = 31)
Age (years)	13.9 (4.0)	13.9 (3.0)	13.8 (2.7)
Gender	40 M / 7 F	10 M / 1 F	28 M / 3 F
Verbal IQ	98.9 (21.3)	49.9 (10.7)	112.5 (12.9)
Nonverbal IQ	105.5 (16.7)	53.1 (14.8)	111.4 (12.6)
Social Responsiveness Scale			
T-Score	73.8 (8.6)	75.1 (8.7)	58.1 (4.4)
Repetitive Behavior Scale—Revised			
Stereotyped Behavior	3.7 (2.4)	7.0 (3.2)	.1 (.5)
Self-Injurious Behavior	2.0 (3.0)	3.6 (4.6)	.2 (.5)
Compulsive Behavior	4.2 (4.6)	8.4 (4.3)	.5 (1.5)
Ritualistic Behavior	4.8 (4.0)	6.5 (3.9)	.6 (2.7)
Total	7.2 (6.0)	44.3 (18.0)	1.2 (5.9)
Interest Scale			
Total Severity	13.9 (3.7)	9.0 (3.4)	--
Autism Diagnostic Observation Schedule			
Social + Communication	10.5 (3.5)	8.0 (1.4)	--
Stereotyped Behavior + Restricted Interest	4.0 (2.2)	7.0 (2.8)	--
Total Severity	14.5 (4.7)	8.1 (1.2)	--

ASD, Autism Spectrum Disorder; *TD*; typically developing; *M*, male; *F*; female

Stimuli and task

Preferential Viewing Task

The preferential viewing task was designed for this study and is comprised of 20 static, high-quality color picture arrays. Each array contained a pair of social and object images (refer to Figure 2.1). Static images were used to ensure greater experimental control across our stimulus categories, including accounting for category specific motion differences (e.g., biological vs. mechanical motion) as well as low-level salience properties of the stimuli, such as luminance and image complexity. Further, the use of these static images allowed us to include a contrast of low- and high- autism interest images based on previous experimental results.

The 20 social images were taken with permission from the MacArthur Foundation Research Network on Early Experience and Brain Development (Tottenham et al., 2009). Identities of the faces did not repeat, were split evenly between males and females, and consisted of Caucasian, African-American, and Asian-American. Of the 20 object stimuli, half were selected to represent items frequently occurring as topics of CI in ASD (South, Ozonoff, & McMahon, 2005). Previous work in the lab validated the reward value of these stimuli using standardized valence and arousal ratings. These stimuli were rated by participants with ASD as significantly higher in valence than control object images (Sasson et al., 2012). We have termed these CI-related stimuli "High Autism Interest" (HAI) objects. Examples of HAI objects include: trains, vehicles, airplanes, clocks, and blocks. The remaining objects included control objects, which were not related to CI and which we have found participants with ASD to rate significantly lower in valence (Sasson et al., 2012). We have termed these images "Low Autism Interest" (LAI) objects. Examples of LAI objects include: clothing, tools, musical instruments, and plants. Each

image measured approximately 8 x 10 cm, and images were separated by a gap of approximately 12 cm. Images were also matched for luminance and complexity. Equivalent areas of interest were drawn for social and nonsocial images, and each corresponded to approximately 25% of the total viewing area. Each stimulus array contained one social image paired with one object (either HAI or LAI) image. Positioning (left vs. right) of all stimulus categories was counterbalanced across arrays.

Eye-tracking

Testing occurred in a research laboratory. Participants sat approximately 60 cm from a 1,024 horizontal x 768 vertical 17-inch display and viewed stimuli subtending a visual angle of 16.1 degrees. Eye movements were recorded with a Tobii 1750 eye tracker (Tobii Technology, Stockholm, Sweden). The system uses an infrared light to produce reflection patterns on the corneas of the eye and monitors these reflections relative to the eye's position. This system samples at a rate of 50 Hz. This eye tracking system is mounted on the computer monitor, and therefore does not interfere with data collection. The system allows for head movement within a cubic space of 30x15x20 cm from a distance of 60 cm, allowing the participants to view in a naturalistic manner. The task was preceded by a 5-point calibration procedure, which was repeated until calibration was sufficient for each of the data points. Prior to the task, the participant was told to view the arrays however he/she wanted. Stimulus arrays were then displayed individually for 5 seconds each. Prior to each trial, a blank slide with a fixation cross appeared for 5 seconds to reorient attention and ensure that all scanning patterns began equidistant from each image in the stimulus pair.

Psychometric measures

Social Responsiveness Scale

The Social Responsiveness Scale (SRS; Constantino and Gruber, 2002) is a parent report questionnaire intended to measure behaviors related to social impairment, including social awareness, social information processing, capacity for reciprocal social communication, and social anxiety/avoidance, in children ages 4 to 18 years of age. An additional section of the SRS contains questions regarding autistic preoccupations and traits.

Autism Diagnostic Observation Schedule

The ADOS (Lord et al., 2012) is a semi-structured, play-based diagnostic measure of the core features of ASD. In addition to providing a score to measure against diagnostic thresholds, the ADOS now provides scores of ASD severity (Gotham et al., 2008). These scores can be used to compare severity across ages (ADOS modules) in individuals with ASD.

Repetitive Behavior Scale-Revised

Previous studies have shown a wide variety of repetitive behaviors occur in autism (Bodfish, Symons, Parker, & Lewis, 2000; Honey, Leekam, Turner, & McConachie, 2007; Lam & Aman, 2007). The Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al., 1999; Lam and Aman, 2007) was used to identify the presence of specific subtypes of repetitive behavior. The RBS-R is an informant rating scale that assesses five categories of repetitive behavior (motor stereotypy, repetitive self-injury, compulsions, routines/sameness, restricted interests). These subscales have high internal consistency, with Cronbach's alpha values ranging from .78 (restricted interests) to .91 (routines/sameness) (Lam & Aman, 2007).

Interest Scale

The Interest Scale (Turner-Brown et al., 2011) is used to collect detailed information on the presence and severity of circumscribed interests. This scale contains a checklist of interests, for which parents indicate if these are currently or have ever been an interest of their child; these are summed separately to indicate the number of past interests and number of current interests the child has endorsed. Additional questions characterize the child's strongest interest, including the degree to which this interest is shared with other people (social involvement), and the flexibility, frequency, intensity, interference, and accommodation of that specific interest, which are combined to produce a total severity score (range 0-23; higher score indicates greater severity).

Eye-tracking variables

Eye-tracking data was analyzed to look at a variety of gaze components. These variables were averaged across social images and object images, within array types, resulting in four dependent variable categories for each eye-tracking variable: SOC + LAI: Social, SOC + HAI: Social, SOC + LAI: Object, and SOC + HAI: Object. Eye-tracking patterns were analyzed as a result of conducting fixation analyses. Fixations were classified using the Tobii Studio I-VT filter, which defines fixations as gaze moving at a velocity slower than 30 degrees per second, for at least 60 milliseconds. Four dependent variables were extracted from the data collected: (a) Prioritization: the latency to first fixate on each stimulus type, which measures attention capture and orienting; (b) Location: the percent of times the first fixation landed on social images, which measures initial attentional bias; (c) Preference: the proportion of on screen fixation time devoted to each image type, relative to total time spent on the stimulus array; and (d) Detail orientation: the

average number of discrete fixations the participant makes on each stimulus type, relative to total time on the array, across arrays.

Statistical analysis

Repeated measures analysis of variance (RM-ANOVA) was conducted on each of the primary variables, with object type (LAI or HAI) as the within-subjects variable and group (TD, ASD, ASD+ID) as the between groups variable. A significant interaction for any of the dependent variables would suggest that one object type disproportionately influences attention, compared to the other. All significant interactions were followed up with post-hoc analyses to identify the direction of the effect. Between-group effects were followed-up with post-hoc t-tests. Separate RM-ANOVA analyses were conducted for each variable.

Spearman's rank order correlations (Spearman's rho) were used to assess relationships between eye-tracking variables and psychometric data. This approach was established based on non-normality of the data.

Results

Feasibility: Analysis of task performance

The nature of the paired preference task requires that each participant is looking at the stimulus for a sufficient amount of time to observe both images. Therefore, I developed a method to exclude participants based on insufficient total look time per trial, in order to eliminate potential bias from the data. Any trials for which viewing time was less than 2.5 seconds was excluded from analyses. Further, participants had to maintain at least 3 trials per condition (30%) for his or

her data to be included in final analyses. A participant was only included in the analysis if the minimum data criteria was met for both SOC+LAI and SOC+HAI trials. Applying these criteria resulted in exclusion of 13 participants with ASD (27%), 3 participants with ASD+ID (27%), and 6 participants with TD (15%).

Univariate ANOVAs were conducted to determine between-group differences for trial inclusion across array types (Figure 4.1). There was a significant effect of group for both SOC+LAI ($F(2, 72) = 3.542$, $p = .034$) and SOC+HAI ($F(2, 72) = 5.647$, $p = .005$) trials. Follow-up t-tests revealed that participants with ASD+ID contributed significantly fewer trials than both TD and ASD peers for both stimulus categories. Paired samples t-tests were conducted to determine within-group differences for trial inclusion. Participants with TD contributed significantly fewer SOC+LAI trials than SOC+HAI trials ($t = -2.556$, $p = .016$). Participants with ASD and ASD+ID did not differ in number of trials included between conditions (ASD, $t = -1.883$, $p = .068$; ASD+ID, $t = -.145$, $p = .889$).

Figure 4.2 provides a visual representation of data quality from all 13 participants in the ASD+ID group, displayed separately for SOC+LAI vs. SOC+HAI trials. Bars indicate the number of included trials, per participant, according to the previously mentioned trial inclusion criteria. Based on these results, only participants with 30% or greater rates of inclusion were included in further analyses.

Group differences: Eye-tracking variables

Prioritization – Social

A 3x2 (Group: ASD, ASD+ID, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for social prioritization (i.e. the latency to first fixation on a social image; see Figure 4.3). There was no group x array interaction ($F(2, 72) = .797$, $p = .453$). There was a marginal main effect of array ($F(1, 72) = 3.753$, $p = .057$), with trends indicating increased latency for social information for SOC+HAI arrays, compared to SOC+LAI. There was no main effect of group ($F(1, 72) = 2.16$, $p = .121$). Group effect trends were explored more thoroughly with follow-up post-hoc t-tests.

For SOC+LAI arrays, participants with ASD+ID did not significantly differ from ASD ($t = -.254$, $p = .801$) or TD ($t = -1.16$, $p = .253$) peers in latency to view social images. Participants with ASD also did not differ from TD peers ($t = -1.37$, $p = .176$). For SOC+HAI arrays, participants with ASD+ID did not differ significantly from ASD peers ($t = .574$, $p = .651$) or TD peers ($t = .747$, $p = .262$), although trends in the data indicate an increase from the latter. Participants with ASD were significantly delayed in latency to view HAI images, compared to TD peers ($t = -2.083$, $p = .041$).

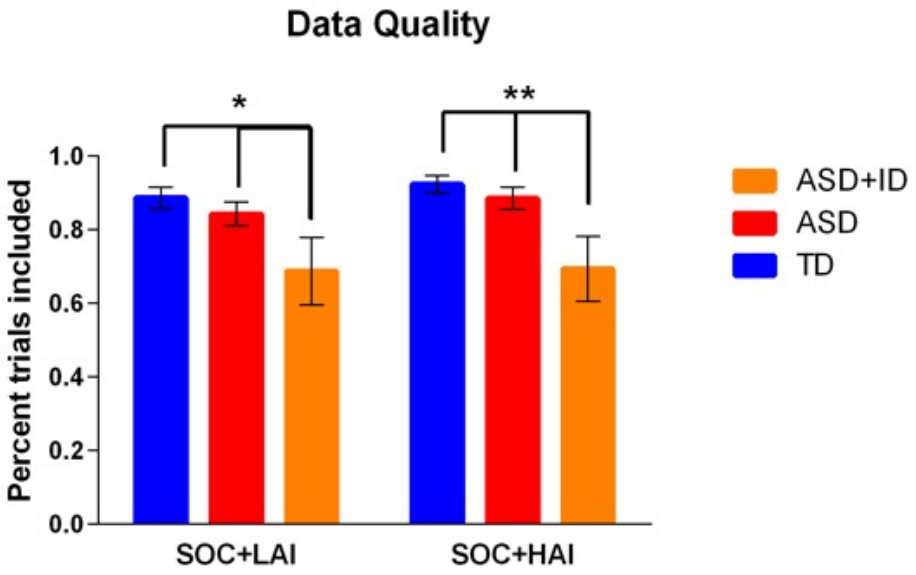

Figure 4.1 **Data quality for SOC+HAI and SOC+LAI arrays across participants.** Error bars indicate standard error of the mean. *, $p < .05$; **, $p < .01$; *ASD,* Autism Spectrum Disorder; *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

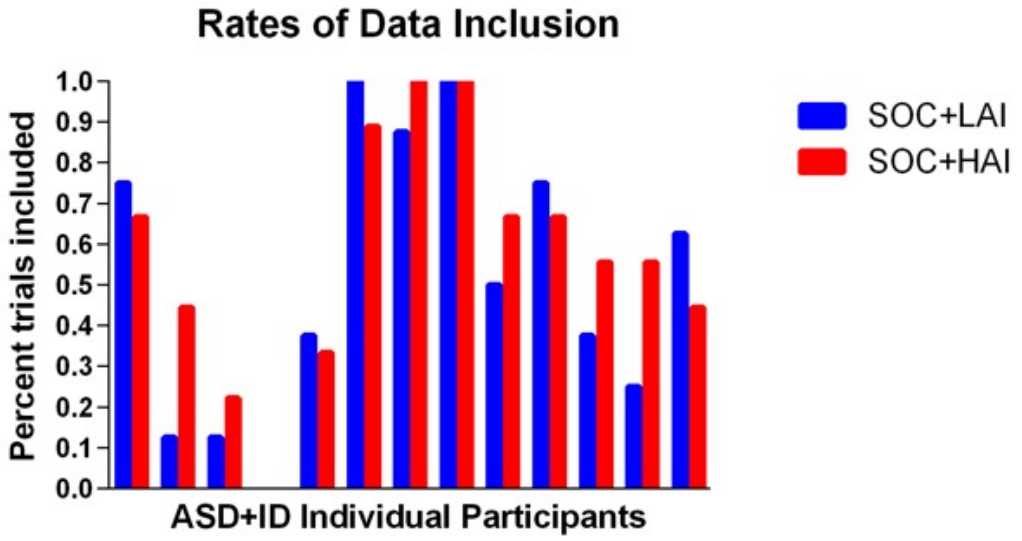

Figure 4.2 **Rates of data inclusion across participants in the ASD+ID subgroup.** *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Location of first fixation

A 3x2 (Group: ASD, ASD+ID, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted to determine the percentage of first fixations that were to social images (Figure 4.4). There was no group x array interaction ($F(2, 72) = 1.003$, $p = .372$). There was no main effect of array ($F(1, 72) = 1.56$, $p = .215$). There was no main effect of group ($F(1, 72) = 1.65$, $p = .206$). Group effect trends were explored more thoroughly with follow-up post-hoc t-tests.

For SOC+LAI arrays, participants with ASD+ID showed no difference in location of first fixation from ASD ($t = 1.56$, $p = .127$) and significant differences from TD ($t = 2.37$, $p = .022$) peers. These results indicate that participants with ASD+ID looked first to faces less frequently than participants with TD. Participants with ASD did not differ from TD peers in first fixation location ($t = 1.10$, $p = .276$). For SOC+HAI arrays, participants with ASD+ID showed no differences from ASD ($t = 1.62$, $p = .114$) and significant differences from TD ($t = 2.88$, $p = .006$), indicating fewer initial fixations to faces in the ASD+ID group. Participants with ASD displayed a similar trend, making marginally fewer initial fixation to faces during SOC+HAI trials, compared to TD ($t = 1.819$, $p = .074$).

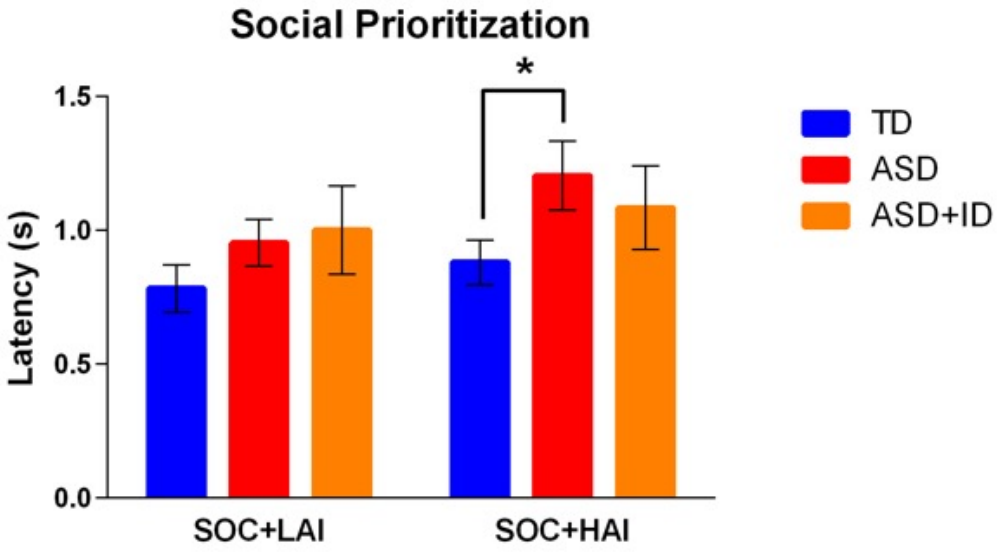

Figure 4.3 **Average latency to first fixate on social images in TD, ASD, and ASD+ID participants.** Error bars indicate standard error of the mean. *, $p < .05$; *ASD,* Autism Spectrum Disorder; *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

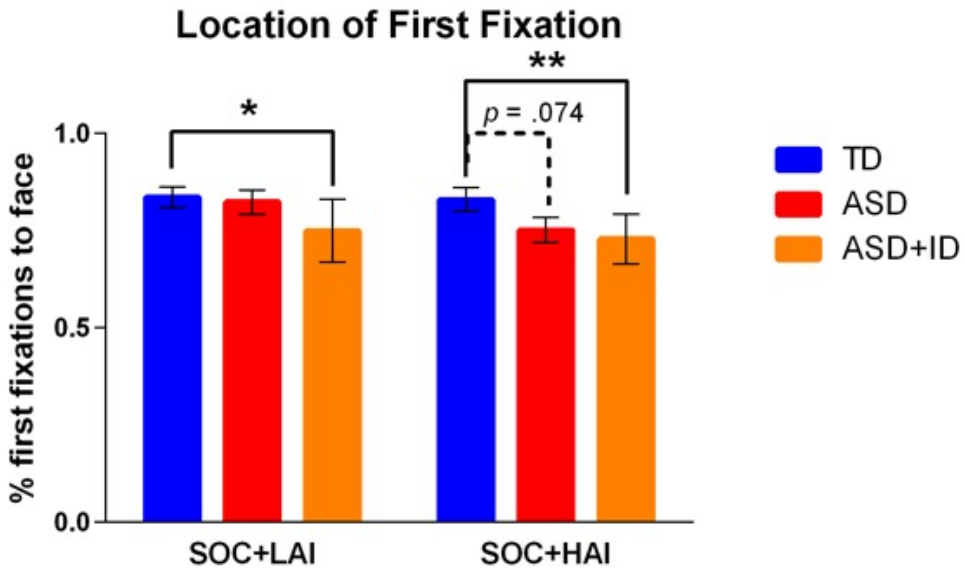

Figure 4.4 **Proportion of initial fixations to social images in TD, ASD, and ASD+ID participants.** Error bars indicate standard error of the mean. *, $p < .05$; **, $p < .01$; *ASD,* Autism Spectrum Disorder; *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Preference – Social

A 3x2 (Group: ASD, ASD+ID, TD; Array: SOC + LAI, SOC + HAI) RM-ANOVA was conducted for social preference (i.e. proportion of all fixations that were to social images, see Figure 4.5). There was a marginally significant group x array interaction ($F(2, 72) = 2.93$, $p = .060$). There was a main effect of array ($F(1, 72) = 31.868$, $p < .001$), indicating that across groups, participants looked more to social images in SOC+LAI arrays than in SOC+HAI arrays. There was a main effect of group ($F(1, 72) = 8.08$, $p = .001$).

Post-hoc t-tests were conducted to determine the nature of the interaction and group-differences. For SOC+LAI arrays, participants with ASD+ID differed significantly in social preference from ASD ($t = -2.395$, $p = .021$), but not TD ($t = .052$, $p = .95$) peers. Further, participants with ASD differed significantly from TD peers ($t = 3.95$, $p < .001$). These results indicate that both ASD+ID and TD participants demonstrated increased social preference, compared to ASD. For SOC+HAI arrays, participants with ASD+ID did not differ from ASD for social preference ($t = -.445$, $p = .659$). However, both ASD subgroups differed from TD (ASD+ID, $t = 1.78$, $p = .085$; ASD, $t = 3.32$, $p = .001$). These results indicate that, unlike social preference as measured in the SOC+LAI arrays, both ASD and ASD+ID groups displayed significantly reduced social preference as measured in the SOC+HAI arrays, compared to TD.

One-sample t-tests were conducted to determine statistical significance from zero. Significant results values greater than .5 indicate preference for social information, while values less than .5 indicate preference for nonsocial information. For SOC+LAI arrays, participants with ASD+ID did not demonstrate preference for either stimulus ($t = 1.02$, $p = .34$). Participants with ASD

demonstrated a clear nonsocial preference (t = -3.31, p < .001), while participants with TD demonstrated a clear social preference (t = 2.24, p = .033). For SOC+HAI arrays, both ASD+ID (t = -2.45, p = .04) and ASD (t = -5.38, p < .001) demonstrated a clear nonsocial preference, while participants with TD showed no preference (t = -.656, p =.517).

Detail Orientation – Social

A 3x2 (Group: ASD, ASD+ID, TD; Array: SOC + LAI, SOC + HAI) Repeated measures RM-ANOVA was conducted for social detail orientation (i.e. number of discrete fixations to social images, see Figure 4.6). There was no group x array interaction (F(2, 72) = 1.54, p = .222). There was a main effect of array (F(1, 72) = 32.719, p < .001), indicating that across groups, participants made more fixations to social images in SOC+LAI arrays than in SOC+HAI arrays. There was a main effect of group (F(1, 72) = 6.18, p = .003).

Post-hoc t-tests revealed that for SOC+LAI arrays, participants with ASD+ID did not differ from TD (t = .321, p = .75) in number of fixations. Participants with ASD demonstrated significantly fewer social fixations than both ASD+ID (t = -2.045, p = .052) and TD (t = 2.715, p = .009) participants. For SOC+HAI arrays, participants with ASD+ID did not differ from ASD (t = -.480, p = .634). Both ASD groups made significantly fewer fixations to faces than TD groups (ASD+ID, t = 2.315, p = .033; ASD, t = 3.32, p = .001).

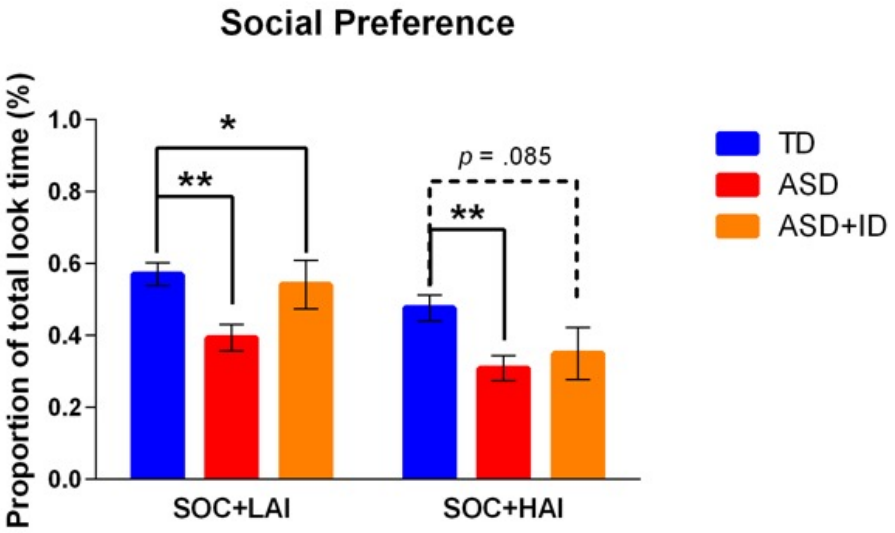

Figure 4.5 **Average proportion of total look time to social images for TD, ASD, and ASD+ID participants.** Error bars indicate standard error of the mean. *, $p < .05$; **, $p < .01$; *ASD,* Autism Spectrum Disorder; *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

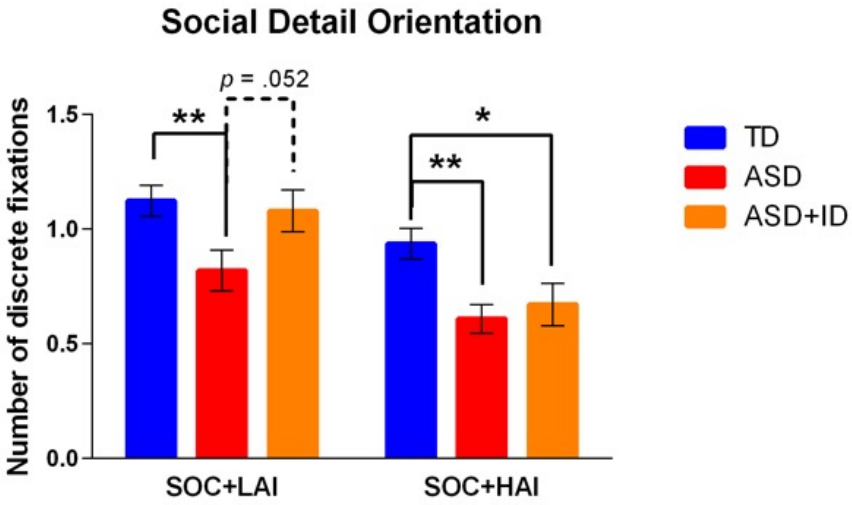

Figure 4.6 **Average number of fixations to social images in TD, ASD, and ASD+ID participants.** Error bars indicate standard error of the mean. *, $p < .05$; **, $p < .01$; *ASD,* Autism Spectrum Disorder; *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Correlations: Eye-tracking variables and psychometric measures

Spearman's rank order correlation analyses were conducted for participants with ASD+ID only, between all eye-tracking variables and psychometric measures indicated in Table 4.1. A significant correlation was observed between the location of first fixation to social images in SOC+HAI arrays and severity of circumscribed interests, as indexed by the Interest Scale (Figure 4.7; ρ = -.902, p = .002). This correlation indicates that participants who had higher severity scores (indicating that the interest of the participant was associated with decreased flexibility and social inclusion, interfered more significantly with other activities, and required increased accommodation) directed their first fixation less frequently to social images. In other words, these participants directed their first fixation *more* frequently to *nonsocial* images, specifically for HAI nonsocial images.

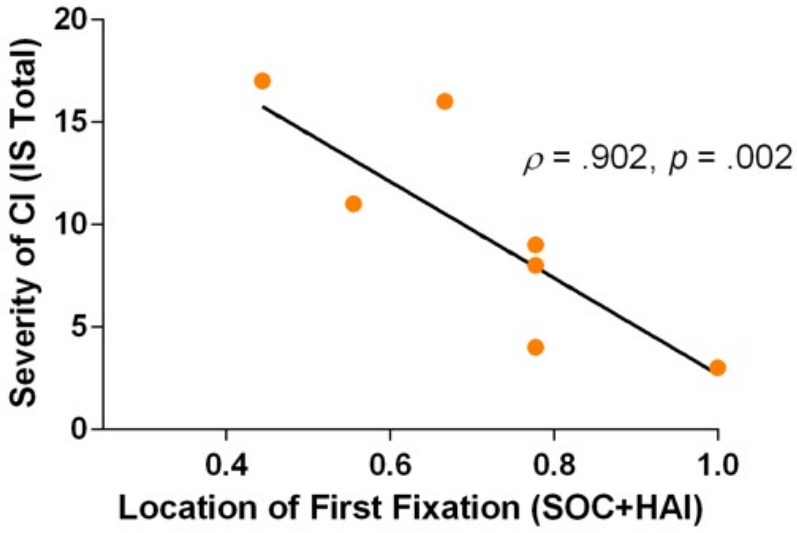

Figure 4.7 **Correlation between circumscribed interest severity and social attention in ASD+ID participants.** *ASD+ID*, Autism Spectrum Disorder with co-morbid intellectual disability; *SOC*, social; *HAI*, high autism interest; *CI*, circumscribed interest; *IS*, Interest Scale

Discussion

The purpose of this study was to expand a previously established eye-tracking task to a sample of individuals with ASD and co-occurring diagnosis of intellectual disability (ID). Importantly, it is currently unknown whether findings from studies including only individuals with ASD and average IQ can, or should, be extrapolated to further our understanding of individuals who comprise nearly half of the ASD population. Here, I present data from a preferential viewing task, which can be used to assess visual preference and gaze dynamics to social and nonsocial stimuli. In general, the most evidence for consistency in performance between the ASD and ASD+ID subgroups was found for measures of social attention and preference during conditions where social images competed for attention with high autism interest nonsocial images. In addition, participants with ASD and ASD+ID differed in social attention measures during SOC+LAI arrays, suggesting potential distinctions in how varieties of nonsocial information are processed between these subgroups.

Feasibility for this task was assessed both across groups and across stimulus conditions. First, I confirmed that overall inclusion rates between ASD and ASD+ID groups were comparable, indicating that participants with comorbid ID were equally capable of meeting minimum inclusion criteria to be included in data analysis. However, subsequent analysis indicated that of participants who were included in analysis, those with ASD+ID contributed fewer trials than peers with ASD and average IQ. This indicates that while participants with ASD+ID contributed sufficient data, this data was sparser than data provided by ASD and TD peers.

The current feasibility data provides insight into potential future modifications of this task. For example, participants with ASD+ID may benefit from shorter duration of trials, which would not require the same extent of sustained attention as the current trial length. It is possible that the length of 5 seconds per trial is longer than necessary to measure orienting and preference; however, future studies are needed to address the minimum viewing time to obtain a valid assessment, as a critical aspect of this task is a forced choice in viewing time between two images. Similarly, future studies are required to determine the minimum number of trials necessary to obtain valid measurement of these variables. Finally, future studies may benefit from incorporating strategies of attention capture during inter-stimulus intervals. This may be accomplished by utilizing a dynamic fixation target (i.e. fixation dot that pulses in size or spinning cross). A more salient directive toward the center of the screen will ensure increased trial validity (and therefore data inclusion) across participants, but may be particularly useful for participants with ASD+ID. This strategy has proven to be successful in existing eye-tracking studies of infants and other individuals with low IQ or developmental level (Sasson & Elison, 2012).

Social preference was measured as the proportion of time participants viewed social images, compared to nonsocial images. Participants with ASD+ID showed increased social preference in SOC+LAI arrays, compared to SOC+HAI arrays; in effect, this group showed more "typical-like" viewing patterns for the former vs. more "ASD-like" for the latter. To clarify the nature of this viewing pattern, independent samples t-tests were conducted to determine if preference differed from 50%, or essentially equal preference for both images. For SOC+LAI arrays, these tests revealed a clear social preference for TD participants and a clear nonsocial preference for

ASD participants, while ASD+ID participants showed no clear preference. For SOC+HAI arrays, however, participants with ASD+ID demonstrated attentional patterns that were similar to ASD peers, with both groups showing clear nonsocial preference. As the nature of the preferential viewing task is to assess context-dependent attention, this pattern of results suggests that participants with ASD+ID may have been more influenced by the presence of CI-related (HAI) images than their ASD peers with no co-occurring ID. This result is supported by a similar pattern reflected in social detail orientation, such that participants with ASD+ID show significant modulation in number of fixations to social images across array types.

Taken together, it appears that participants with ASD+ID are consistently slower to attend to social information than ASD peers with no co-occurring ID and demonstrate social attention that is significantly influenced by the presence of CI-related information, even compared to ASD peers. Thus, the types of nonsocial attentional bias found in previous studies of individuals with ASD and average intelligence appear to generalize to those with co-occurring intellectual disability, who may show an even greater degree of nonsocial bias than their average IQ peers. Although in general there was evidence for consistency in results between the ASD and ASD+ID subgroups on this task, participants with ASD+ID also demonstrated some clear deviations from ASD only participants that may represent important mechanistic and / or developmental differences.

A significant correlation was observed between circumscribed interest severity, as measured by the Interest Scale, and location of first fixation for SOC+HAI arrays. This indicated that participants who made fewer first fixations to social images (and therefore more first fixations to

HAI images) had higher severity scores. The Interest Scale calculates a severity score based on the primary interest of the participant. The informant (parent or caregiver) then ranks the interest on several domains of adaptive behavior. These domains include the degree to which the interest interferes with other activities (e.g., the individual refuses to eat because he is busy engaged in preferred activity), the amount of accommodation provided for the individual to engage in the interest (e.g., family vacations must be centered around this interest), the degree of resistance when interrupted (e.g., tantrums, self-injurious behavior), the degree of flexibility in the interest (e.g., child will only play with small, blue blocks), and the amount of social inclusion (e.g., an individual enjoys games on his iPad, but only when playing by himself). Although increased sample size is necessary to further interpret this result, these results suggest that dimensional measures of a reward-related endophenotype taken from an eye-tracking task relate to differences in the clinical phenotype of persons with ASD+IDD.

Approximately 30% of individuals with ASD express what is known as "minimal verbal ability," which loosely describes the group of individuals who have not acquired flexible use of spoken language by age 5 (Tager-Flusberg & Kasari, 2013; Anderson, 2007). While there is an important distinction between ASD+ID and minimal verbal ability (i.e. not all participants with limited language also have an ID diagnosis), ASD+ID is associated with greater severity of language deficits (Ellis Weismer & Kover, 2015; Rose et al., 2016). Of note, participants in this study were not recruited based on language ability. However, individual item analysis of ADOS communicative scores indicated that all participants in the ASD+ID group had language abilities that were limited to fewer than 5 words or phrases characterized entirely by echolalia / verbal stereotypy. It is currently unknown why some individuals with ASD never acquire spoken

language. However, a predominant theory suggests that social motivation may play a significant role in differential language outcomes. The social motivation theory hypothesizes that an early lack of motivation to attend to or engage with social information contributes to a deficit in social experiences, and therefore, lack of experience that is critical for the development of socio-communicative behaviors. While based on only a small sample, the results of the present study are consistent with this model as participants with ASD+ID, all of whom were minimally verbal, demonstrated relatively greater indices of deficient social motivation (and enhanced nonsocial motivation) than ASD peers without cognitive or language deficits.

This result is also consistent with a previous study that found early deficits in social motivation predicted the degree of later language impairment in ASD (Bopp, Mirenda, & Zumbo, 2009). Here, I demonstrated a potential marker for social motivation deficits that appears to be feasible for assessing individuals at very low levels of general cognitive ability. Given the paucity of quantitative, objective, and dimensional measures of social motivation, the present task may be particularly useful in future studies of language development, and for application to experiments that could more directly test the hypothesis that social motivation (and social orienting) plays a critical role in language deficiencies in persons with autism who are at risk for severe language deficits.

From a clinical perspective, the results of the present study may have most relevance to the area of augmentative and alternative communication (AAC). Visual aides are a primary strategy for communication and adaptive support for individuals with ASD+ID and / or severe expressive language deficits (Mirenda, 2008). These aides may help to structure schedules, support choice-

making behavior, and facilitate voice output systems (Gillespie-Smith & Fletcher-Watson, 2014). Therefore, the ability to attend to relevant visual information, particularly when this information is integrated into an interaction with another person (e.g., teacher), is a critical aspect of therapeutic intervention. Similarly, if social information is intended to be communicated through such supports, it is essential that these images attract the attention of the individual (Gillespie-Smith & Fletcher-Watson, 2014). Results from the current study may have implications for how images on AAC devises are configured for optimal use by persons with ASD+ID. For example, if as found in this study, social information is consistently slower to attract attention, then this could be factored in to AAC design with respect to how choices are presented. Perhaps of more importance are the implications of the present findings with regard to nonsocial information processing and the use of object images on AAC devices. Items related to circumscribed interests are commonly used as items of reinforcement (e.g., Adams, 1999; Kryzak & Jones, 2014) for persons with ASD. Therefore, it would not be uncommon for an individual's visual support to have these images incorporated into its content. However, the presence of nonsocial content may critically detract attention from other – and especially social-communicative – content. In this way, results from eye-tracking studies in ASD+ID may have translational value and inform intervention approaches for this population.

This study has several important limitations. Most notably, the sample size of the ASD+ID group was considerably smaller other comparison groups. This difference has the potential to influence results in two significant ways: first, this study was largely underpowered to detect significant group effects. To account for this, the focus of results and interpretation was based largely on trends, rather than adhering to a strict alpha criterion. However, this brings forth the caveat that

all results should be interpreted as exploratory and require future replication. In this same vein, correlations between visual attention and ASD symptomology in ASD+ID should be interpreted with caution. Importantly, this relationship was not observed for ASD participants with no co-occurring ID. This divergent pattern may reflect differing mechanisms in nonsocial attention between the two groups; however, this finding may also be a factor of differing sample size and not hold true for a more representative sample of participants with ASD+ID.

The current study addresses a significant knowledge gap in the current ASD literature by examining aspects of social motivation in individuals with a range of cognitive ability. The eye-tracking task presented here shows high rates of feasibility and therefore may be one avenue for growing the current knowledge base of how individuals with ASD+ID may differ from peers with average intelligence. This task may specifically address constructs that contribute to clinically significant aspects of ASD, such as the development of functional language, by examining aspects of motivation and reward. Future research using this paradigm may examine sensitivity to treatment differences or examine groups that are stratified by language ability to more specifically address how motivation contributes to the wide rage of language-related differences in ASD.

REFERENCES

Adams, L. W. (1999). *Incorporating narrow interests into the school tasks of children with autism*. University of North Carolina at Chapel Hill.

Bodfish, J., Symons, F., & Lewis, M. (1999). The repetitive behavior scale. *Western Carolina Center Research Reports*.

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders*, *30*(3), 237–243.

Bopp, K. D., Mirenda, P., & Zumbo, B. D. (2009). Behavior predictors of language development over 2 years in children with autism spectrum disorders. *Journal of Speech, Language, and Hearing Research*, *52*(5), 1106–1120.

Brown, A. C., Chouinard, P. A., & Crewther, S. G. (2017). Vision research literature may not represent the full intellectual range of Autism Spectrum Disorder. *Frontiers in Human Neuroscience*, *11*. Retrieved from https://www-ncbi-nlm-nih-gov.proxy.library.vanderbilt.edu/pmc/articles/PMC5306295/

Bryson, S. E., Bradley, E. A., Thompson, A., & Wainwright, A. (2008). Prevalence of autism among adolescents with intellectual disabilities. *The Canadian Journal of Psychiatry*, *53*(7), 449–459.

Constantino, J. N., & Gruber, C. P. (2002). The social responsiveness scale. *Los Angeles: Western Psychological Services*.

Ellis Weismer, S., & Kover, S. T. (2015). Preschool language variation, growth, and predictors in children on the autism spectrum. *Journal of Child Psychology and Psychiatry*, *56*(12), 1327–1337.

Fantz, R. L. (1964). Visual Experience in Infants: Decreased Attention to Familiar Patterns Relative to Novel Ones. *Science*, *146*(3644), 668–670. https://doi.org/10.1126/science.146.3644.668

Gillespie-Smith, K., & Fletcher-Watson, S. (2014). Designing AAC systems for children with autism: Evidence from eye tracking research. *Augmentative and Alternative Communication*, *30*(2), 160–171.

Goren, C. C., Sarty, M., & Wu, P. Y. K. (1975). Visual Following and Pattern Discrimination of Face-like Stimuli by Newborn Infants. *Pediatrics*, *56*(4), 544–549.

Gotham, K., Risi, S., Dawson, G., Tager-Flusberg, H., Joseph, R., Carter, A., … Hyman, S. L. (2008). A replication of the Autism Diagnostic Observation Schedule (ADOS) revised algorithms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(6), 642–651.

Honey, E., Leekam, S., Turner, M., & McConachie, H. (2007). Repetitive behaviour and play in typically developing children and children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(6), 1107–1115.

Johnson, M. H., Dziurawiec, S., Ellis, H., & Morton, J. (1991). Newborns' preferential tracking of face-like stimuli and its subsequent decline. *Cognition*, *40*(1), 1–19.

Kaufman, A. S., & Kaufman, N. L. (2004). *Kaufman brief intelligence test*. Wiley Online Library. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/9781118660584.ese1325/summary

Kim, S. H., Macari, S., Koller, J., & Chawarska, K. (2016). Examining the phenotypic heterogeneity of early autism spectrum disorder: subtypes and short-term outcomes. *Journal of Child Psychology and Psychiatry*, *57*(1), 93–102.

Kryzak, L. A., & Jones, E. A. (2014). The Effect of Prompts within Embedded Circumscribed Interests to Teach Initiating Joint Attention in Children with Autism Spectrum Disorders. *Journal of Developmental and Physical Disabilities*, *27*(3), 265–284. https://doi.org/10.1007/s10882-014-9414-0

Lam, K. S., & Aman, M. G. (2007). The Repetitive Behavior Scale-Revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(5), 855–866.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism diagnostic observation schedule: ADOS-2*. Western Psychological Services Los Angeles, CA.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685.

McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. *Pediatrics*, *133*(5), 872–883.

Mirenda, P. (2008). A Back Door Approach to Autism and AAC. *Augmentative and Alternative Communication*, *24*(3), 220–234. https://doi.org/10.1080/08990220802388263

Nordin, V., & Gillberg, C. (1996). Autism spectrum disorders in children with physical or mental disability or both. I: Clinical and epidemiological aspects. *Developmental Medicine & Child Neurology*, *38*(4), 297–313.

Papadopoulos, N., McGinley, J., Tonge, B., Bradshaw, J., Saunders, K., Murphy, A., & Rinehart, N. (2012). Motor proficiency and emotional/behavioural disturbance in autism and Asperger's disorder: another piece of the neurological puzzle? *Autism*, *16*(6), 627–640.

Rattaz, C., Michelon, C., & Baghdadli, A. (2015). Symptom severity as a risk factor for self-injurious behaviours in adolescents with autism spectrum disorders. *Journal of Intellectual Disability Research*, *59*(8), 730–741.

Rose, V., Trembath, D., Keen, D., & Paynter, J. (2016). The proportion of minimally verbal children with autism spectrum disorder in a community-based early intervention programme. *Journal of Intellectual Disability Research*, *60*(5), 464–477.

Sasson, N. J., Dichter, G. S., & Bodfish, J. W. (2012). Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PloS One*, *7*(8), e42457.

Sasson, N. J., & Elison, J. T. (2012). Eye tracking young children with autism. *JoVE (Journal of Visualized Experiments)*, (61), e3675–e3675.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive Behavior Profiles in Asperger Syndrome and High-Functioning Autism. *Journal of Autism & Developmental Disorders*, *35*(2), 145–158.

Tager-Flusberg, H., & Kasari, C. (2013). Minimally verbal school-aged children with autism spectrum disorder: the neglected end of the spectrum. *Autism Research*, *6*(6), 468–478.

Tonnsen, B. L., Boan, A. D., Bradley, C. C., Charles, J., Cohen, A., & Carpenter, L. A. (2016). Prevalence of Autism Spectrum Disorders Among Children With Intellectual Disability. *American Journal on Intellectual and Developmental Disabilities*, *121*(6), 487–500. https://doi.org/10.1352/1944-7558-121.6.487

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249.

Turner-Brown, L. M., Lam, K. S. L., Holtzclaw, T. N., Dichter, G. S., & Bodfish, J. W. (2011). Phenomenology and measurement of circumscribed interests in autism spectrum disorders. *Autism*, *15*(4), 437–456. https://doi.org/10.1177/1362361310386507

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W. (2016). Social Orienting and Attention Is Influenced by the Presence of Competing Nonsocial Information in Adolescents with Autism. *Frontiers in Neuroscience*, *10*.

Valenza, E., Simion, F., Cassia, V. M., & Umiltà, C. (1996). Face preference at birth. *Journal of Experimental Psychology: Human Perception and Performance*, *22*(4), 892–903. https://doi.org/10.1037/0096-1523.22.4.892

CHAPTER 5

TYPICAL PATTERNS OF SOCIAL ATTENTION CHANGE WITH AGE IN TYPICAL DEVELOPMENT AND ARE DECREASED IN DEVELOPMENTAL-LEVEL MATCHED PEERS WITH AUTISM

Introduction

The preferential viewing task utilizes eye-tracking to quantify the modulation of visual preference for images, based on their contextual presentation. The use of this task in a sample of adolescents with autism spectrum disorder (ASD) has previously been described (Unruh et al., 2016). Notably, this study demonstrated that adolescents with ASD spent significantly less time looking to social images compared to nonsocial images. Further, in the ASD group only, the presence of a specific category of nonsocial images (those associated with circumscribed interests) was associated with a significant increase in the latency to first attend to social information. These specific findings may have profound implications within a developmental context, as they suggest that individuals with ASD may be significantly impaired in their ability to attend to social information, compared to their typically developing peers, in the context of certain types of nonsocial information that may be highly rewarding. However, to date the developmental implications of this model of social and nonsocial motivation in ASD have not been examined in depth. The current study sought to expand on previous studies by including a downward extension of our previous work to developmentally and chronologically younger participants and modifying the task in an attempt to make it more age-appropriate for infants and toddlers.

Preferential viewing tasks are brief in nature and place minimal task demands on participants; therefore, such a task is an ideal candidate for translation into developmental contexts, especially for evaluating infants or individuals who may not have yet developed language. Behavioral paired image paradigms have been used to assess preference in typically developing children as early as infancy (Valenza, Simion, Cassia, & Umiltà, 1996), and with eye-tracking as early as 3 months of age (e.g., Kelly et al., 2007; Libertus & Needham, 2014). The majority of previous studies have used paired image viewing paradigms to assess preference for faces (e.g., human vs. other species or visual configurations; across race categories), discrimination between two stimulus categories (e.g., Colombo, Mitchell, & Horowitz, 1988), or the effects of habituation (e.g., Rose, Gottfried, Melloy-Carminar, & Bridger, 1982). Therefore, while social attention is well understood in typically developing children, only one study to-date has examined the effects on highly preferred and highly salient nonsocial information on social attention in a preferential viewing paradigm (Sasson & Touchstone, 2014).

Previous studies of face preference have found that infants prefer to view human faces, even over images that contain similar visual characteristics to faces (Goren, Sarty, & Wu, 1975; Johnson, Dziurawiec, Ellis, & Morton, 1991; Valenza et al., 1996). Within the first few months of life, an infant grows to show preference for his mother's face (Pascalis, de Schonen, Morton, Deruelle, & Fabre-Grenet, 1995) and to faces of similar race to the environment in which he grows up (Kelly et al., 2005, 2007). Studies such as these emphasize the important of experience on the development of patterns of visual attention. However, studies have also shown that social attention can change across time. For example, Libertus and colleagues demonstrated an inverted

U-shaped pattern of attention to faces, when paired with a novel object item, such that 5 and 9 month infants showed significantly stronger social preference than 3 and 11 month olds. Further, attention to faces was increased in infants compared to adults. This suggests a developmental trend within social information, as well as the importance of the context in which social information is presented.

Two additional previous studies, to date, have assessed contextual social attention in young children with typical development, in comparison to those with ASD. Elison et al (2012) analyzed the effect of age on visual exploration in arrays containing both social and nonsocial images. This study found increases in visual exploration of both social and nonsocial information in a cross-section of typically developing children from ages 34 to 207 months. Children with ASD also showed an increase in visual exploration of social information, but to a lesser degree. Sasson and Touchstone (2014) added to this literature by presenting visual arrays containing face and object pairs to young children with typical development and ASD. This study observed a greater degree of social attention in typically developing children than those with ASD, only when faces were paired with images of a relatively neutral valence. However, this study also included a manipulation of the affect of faces, which may have disproportionately influenced visual attention in either of the groups.

The overarching purpose of this study was to add to and improve upon previous literature by measuring context-dependent social attention in infants and toddlers with typical development and with ASD. This study had three primary aims. The first aim was to determine the feasibility of a preferential viewing task in a cross-section of children with typical development and ASD,

ranging from 12 months to 60 months. Second, I sought to determine how social attention may change over time in typical development, as a factor of chronological age and gender. Based on previous knowledge of social and novel object attention across development, it was hypothesized that typically developing children would show age-related decreases in social attention across array types. The third aim was to compare patterns of social attention between toddlers with ASD and typically developing developmental age-matched peers. It was hypothesized that children with ASD would show decreased social attention and increased nonsocial attention compared to this sample of younger typically developing peers at a comparable developmental level.

Methods

Participants

For primary aims in typical development, 34 children with typical development (TD; mean age = 37.3 months, range = 26-56 months) were recruited. All participants met the following general inclusion criteria: age between 24 and 60 months; a score of less than 15 on the Social Communication Questionnaire, which was used to screen any potentially unidentified cases of ASD; absence of seizure disorder, acute medical, or genetic condition; and absence of any known visual impairment uncorrectable with eyeglasses. An additional sample of 17 children with typical development (TD-Match; mean age = 15.7 months, range = 12-21 months) were recruited to serve as a comparison group to a recruited sample of 14 children with ASD (mean age = 47.5 months, range = 29-84 months). These groups were matched on scores of developmental level, derived from the Adaptive Behavior Assessment System (ABAS; Harrison & Oakland, 2003). For this set of analyses, all participants with typical development met the

following general inclusion criteria: a score of less than 8 on the Modified Checklist for Autism in Toddlers (Robins, Fein, & Barton, 1999), which was used to screen risk for ASD; absence of seizure disorder, acute medical, or genetic condition; and absence of any known visual impairment uncorrectable with eyeglasses. All participants with ASD met the following inclusion criteria: documented diagnosis of an autism spectrum disorder by a physician or licensed clinician, in addition to meeting criteria for an autism spectrum disorder on an independent assessment of the Autism Diagnostic Observation Schedule (ADOS), which was administered at the time of testing. Participant demographics are described in Table 5.1.

Table 5.1 *Demographics and Participant Characterization for Study 4*

Characteristic	TD (N = 34)	TD-Match (N = 17)	ASD (N = 14)	t value (*p value*)
Age (months)	37.3 (25-60)	15.7 (12-24)	45.0 (37-60)	--
Gender	19 M / 15 F	14 M / 3 F	13 M / 1 F	--
Adaptive Behavior Assessment System (ABAS)				
Conceptual Domain Score	114.0 (19.4)	102.4 (13.1)	86.3 (21.7)	-1.76 (*.111*)

ASD, Autism Spectrum Disorder; *TD*; typically developing; *TD*-Match, typically developing participants matched on developmental-level to ASD; M, male; *F*; female

Stimuli and Task

Preferential Viewing Task

The preferential viewing task described here is comprised of 20 static, high-quality color picture arrays. Each array contained a pair of social and object images. Static images were used to ensure greater experimental control across our stimulus categories, including accounting for category specific motion differences (e.g., biological vs. mechanical motion) as well as low-level salience properties of the stimuli, such as luminance and image complexity. Further, the use of these static images allowed us to include a contrast of low- and high- autism interest images based on previous experimental results.

The 20 social images were taken with permission from the MacArthur Foundation Research Network on Early Experience and Brain Development (Tottenham et al., 2009). Identities of the faces did not repeat, were split evenly between males and females, and consisted of Caucasian, African-American, and Asian-American. Of the 20 object stimuli, half were selected to represent items frequently occurring as topics of CI in ASD (South, Ozonoff, & McMahon, 2005). Previous work in our lab has validated the reward value of these stimuli using standardized valence and arousal ratings. These stimuli were rated by participants with ASD as significantly higher in valence than control object images (Sasson, Dichter, & Bodfish, 2012). We have termed these CI-related stimuli "High Autism Interest" (HAI) objects. Examples of HAI objects include: trains, vehicles, airplanes, clocks, and blocks. The remaining objects included control objects, which were not related to CI and which we have found participants with ASD to rate significantly lower in valence (Sasson et al., 2012). We have termed these images "Low Autism Interest" (LAI) objects. Examples of LAI objects include: clothing, tools, musical instruments,

and plants. Images in this task were modified from the previously described task so that HAI and LAI images were more perceptually similar. Modifications included: replacement of images with visible words / text, or removal of text if it did not change the integrity of the image, and inclusion of LAI images that were more visually salient than in previous version of the task (e.g., replacement of gray work gloves with red polo shirt). Adobe Photoshop was used to measure and adjust luminance of all individual object images so that each condition had approximately equivalent average luminance (LAI mean = 20.94 lux, SD = 4.58; HAI mean luminance = 21.74, SD = 11.60). Adjustments were made such that images had relatively equivalent average luminance, but the integrity of the image was not disrupted (e.g., yellow school bus maintained typical color as to not increase salience because of atypical appearance).

Each image measured approximately 8 x 10 cm, and images were separated by a gap of approximately 12 cm. Equivalent areas of interest were drawn for social and nonsocial images, and each corresponded to approximately 25% of the total viewing area. Each stimulus array contained one social image paired with one object (either HAI or LAI) image. Positioning (left vs. right) of all stimulus categories was counterbalanced across arrays.

Eye-tracking

Testing occurred in a research laboratory. Participants sat approximately 60 cm from a 1,024 horizontal x 768 vertical 17-inch display and viewed stimuli subtending a visual angle of 16.1 degrees. Eye movements were recorded with a Tobii X2-60 eye tracker (Tobii Technology, Stockholm, Sweden). The system uses an infrared light to produce reflection patterns on the corneas of the eye and monitors these reflections relative to the eye's position. This system

samples at a rate of 60 Hz. This eye tracking system is mounted on the computer monitor, and therefore does not interfere with data collection. The system allows for head movement within a cubic space of 30x15x20 cm from a distance of 60 cm, allowing the participants to view in a naturalistic manner.

Participants sat independently or in the lap of a caregiver, depending on age, height, and preference. If the caregiver was present during data collection, he or she was positioned out of range (distance) from the eye-tracker and was asked to refrain from referencing anything on the screen. Each testing session began with a popular children's video, during which no data was collected. This allowed the child time to become familiar with the room and gave the experimenter the opportunity to make adjustments to the child's position and ensure the eye-tracker was able to detect the child's eye. The task was preceded by a 5-point calibration procedure, which was repeated until calibration was sufficient for each of the data points. Prior to the task, the participant was told to watch the pictures on the screen. Stimulus arrays were then displayed individually for 5 seconds each. Prior to each trial, a blank slide with a fixation cross appeared for 2-5 seconds to reorient attention and ensure that all scanning patterns began equidistant from each image in the stimulus pair.

Psychometric Measures

Adaptive Behavior Assessment Scale

The Adaptive Behavior Assessment System (ABAS; Harrison & Oakland, 2003) is a behavior rating scale that provides norm-referenced composite scores for 3 domains of adaptive behavior, along with a global adaptive composite. The parent / primary caregiver form is reliable for use in

children ages birth to 5 years of age. The "Conceptual" adaptive domain was used as a measurement of developmental level. This domain assesses communication, functional pre-academic, and self-directive skills.

Eye-tracking variables

Eye tracking patterns were analyzed as a result of conducting fixation analyses. Fixations were classified using the Tobii Studio I-VT filter, which defines fixations as gaze moving at a velocity slower than 30 degrees per second, for at least 80 milliseconds. These criteria were determined as an intermediary value based on prior studies of visual attention in infants and children, given the cross-sectional nature of the sample (Dalton et al., 2005; Merin, Young, Ozonoff, & Rogers, 2007).

Eye-tracking data was analyzed to look at a variety of gaze components. These variables were averaged across social images and object images, within array types, resulting in four dependent variable categories for each eye-tracking variable: SOC + LAI: Social, SOC + HAI: Social, SOC + LAI: Object, and SOC + HAI: Object. Four dependent variables were extracted from the data collected: (a) Prioritization: the latency to first fixate on each stimulus type, which measures attention capture and orienting; (b) Preference: the proportion of on screen fixation time devoted to each image type, relative to total time spent on the stimulus array; (c) Detail orientation: the average number of discrete fixations the participant makes on each stimulus type, relative to total time on the image, across arrays.

Statistical analysis

Primary cross-sectional analyses were conducted using Bivariate (Pearson's r) correlations to assess the relation between age and eye-tracking data. For these analyses, each variable was log-transformed to account for skewness in the distributions and to improve interpretability. Each variable was transformed by a factor of log(x+1) to preserve data points equal to zero, which were meaningful in this ratio data set.

For developmental-level match comparisons, a multivariate ANOVA was performed to determine overall group differences between social attention variables. Second, due to the nature of the task and the small sample size of the groups, paired samples t-tests were performed to assess within-group changes across array types.

Results

Cross-sectional analysis in typical development

Analysis of task performance

I first sought to assess the feasibility of this task in children by calculating the amount of missing data per trial. The total trial length is 5 seconds, which served as the maximum look time. On average, total viewing time for SOC+HAI trials was 3.49 seconds (SD = .70) and SOC+LAI trials was 3.43 seconds (SD = .74). Average look time did not differ between trials ($t(33) = .711$, $p = .48$). There was a significant correlation between chronological age and total viewing time for both SOC+HAI ($r = .489$, $p = .003$) and SOC+LAI trials ($r = .469$, $p = .005$).

Based on these metrics, a minimum trial time was set at 2.5 seconds; trials that did not exceed this threshold were not included in summary scores for participants, and therefore were not included in analyses. A participant's data was included in final analyses if he or she had at least 40% of trials included in the analyses. An average of 7.9 HAI+SOC trials and 7.6 LAI+SOC trials were included per participant. Number of trials included did not differ between array types ($t(33) = 1.234$, $p = .226$). There was a significant correlation between chronological age and the number of trials included for both SOC+HAI ($r = .380$, $p = .027$) and SOC+LAI trials ($r = .372$, $p = .030$).

Social preference, age, and gender

Bivariate (Pearson's r) correlation analyses were performed to assess the relationship between preference for social stimuli and chronological age at time of testing (Figure 5.1). Analyses revealed a significant correlation between age and social preference for SOC+HAI trials ($r = -.553$, $p = .001$) but not for SOC+LAI trials ($r = -.284$, $p = .103$). These data indicate that older participants spent less time viewing social images than younger participants, but only during trials when competing HAI images were present. Correlation analyses were then performed for male and female participants separately, to determine if gender influenced this pattern of results (Figure 5.2). The correlation between age and social preference for SOC+HAI trials remained significant for male-only ($r = -.507$, $p = .027$) and female-only ($r = -.688$, $p = .005$) analyses. This suggests that age-related changes in social attention were similar across genders.

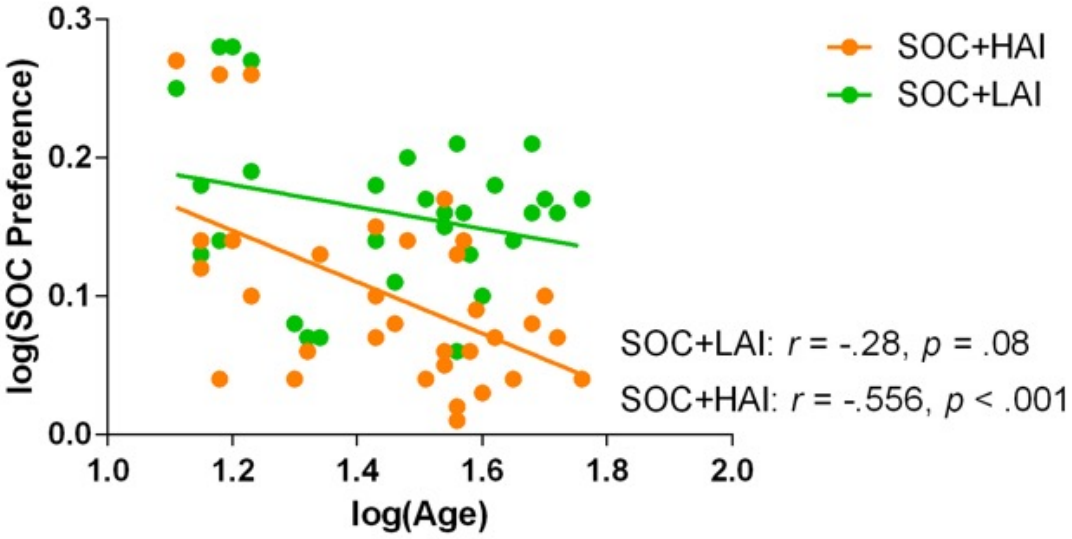

Figure 5.1 **Age-associated decreases in social preference in TD children.** *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

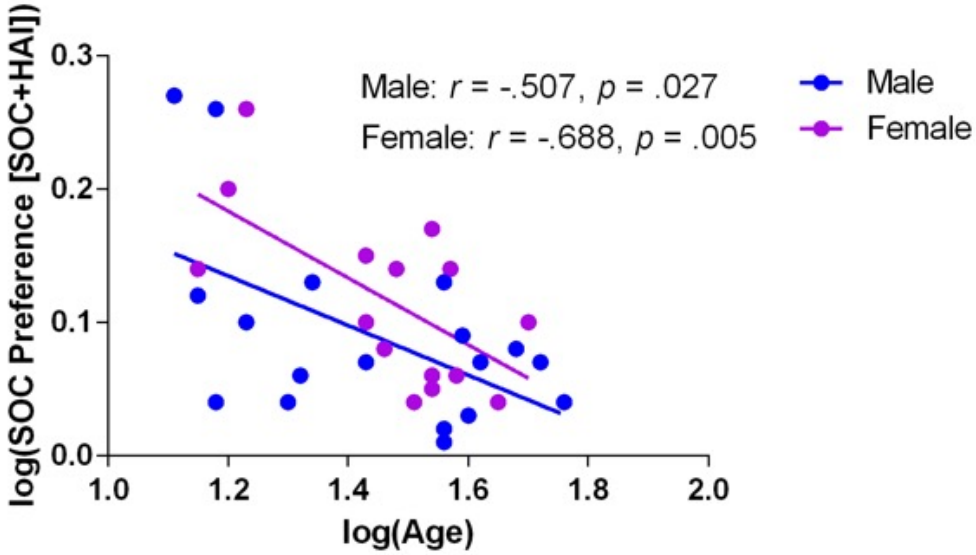

Figure 5.2 **Age-associated decreases in social preference cannot be attributed to TD gender effects.** *TD*, typically developing; *SOC*, social; *HAI*, high autism interest

Social prioritization and age

Bivariate (Pearson's r) correlation analyses were performed to assess the relation between latency to view social stimuli and age at time of testing (Figure 5.3). Analyses revealed a significant correlation between age and social latency for SOC+HAI trials (r = .346, p = .045) and a trend-level correlation for SOC+LAI trials (r = .306, p = .079). These data indicate that older participants took significantly longer to first fixate on social images, than younger participants; however, this effect was only significant for HAI trials.

Social detail orientation and age

Bivariate (Pearson's r) correlation analyses were performed to assess the relation between the number of fixations to social stimuli and age at time of testing (Figure 5.4). Analyses revealed a significant correlation between age and social detail for SOC+HAI trials (r = -.358, p = .038) but not for SOC+LAI trials (r = -.01, p = .995). These data indicate that older participants made significantly fewer fixations to social images than younger participants, when these images were paired with HAI images; this effect was not present in SOC+LAI trials.

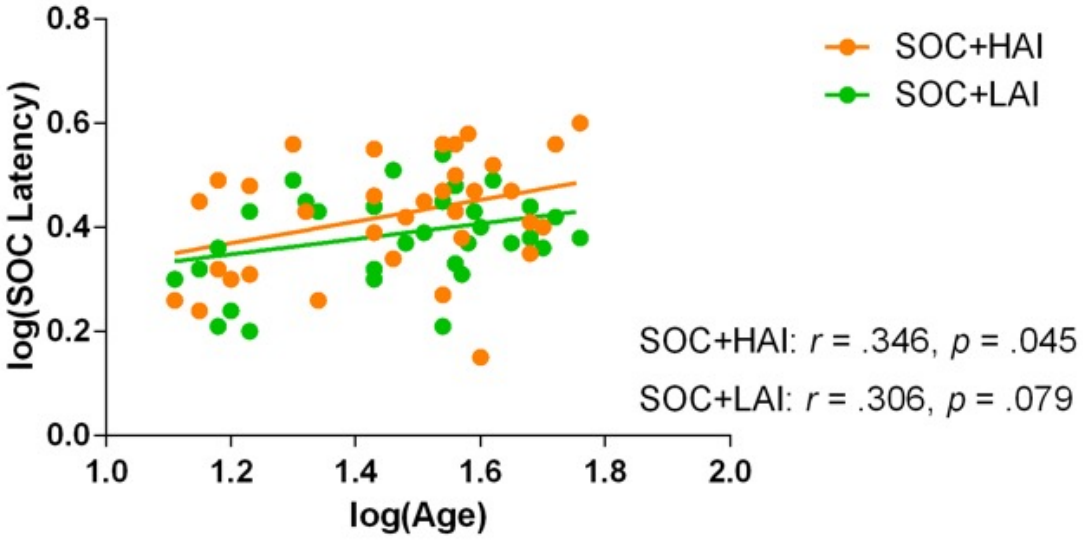

Figure 5.3 **Age-associated changes in social prioritization in TD children.** *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

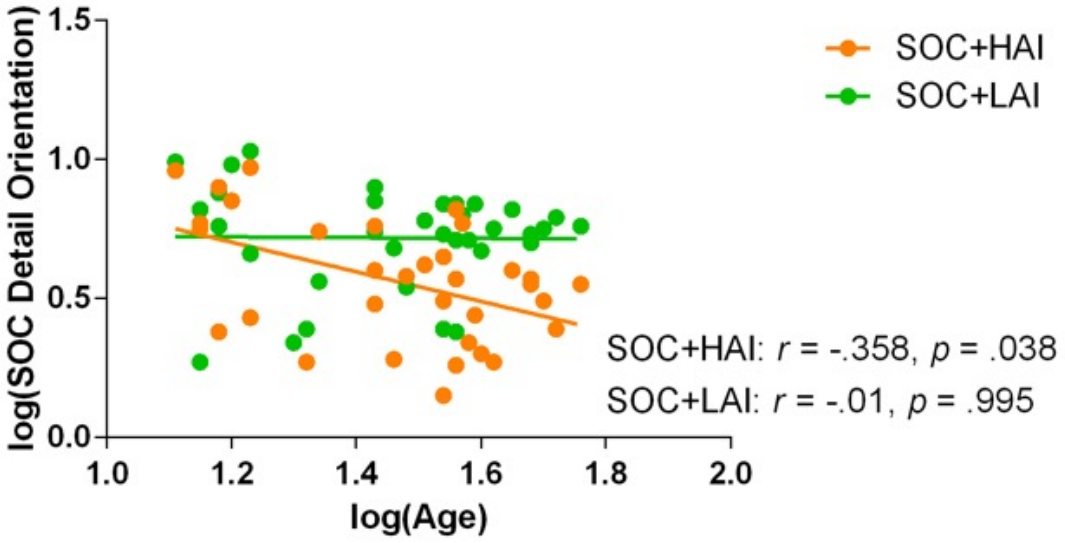

Figure 5.4 **Age-associated changes in social detail orientation in TD children.** *TD*, typically developing; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Comparison of ASD and TD

Analysis of task performance

Task feasibility was determined by assessing the amount of missing data per trial. Total trial length is 5 seconds, which is also the maximum look time. On average, total viewing time for SOC+HAI trials was 2.73 seconds (SD = .94) and SOC+LAI trials was 2.79 seconds (SD = .82). Average look time did not differ between trials ($t(23) = -.418$, $p = .680$).

Based on these metrics, a minimum trial time was set at 2.5 seconds; trials that did not exceed this threshold were not included in summary scores for participants, and therefore were not included in analyses. A participant's data was included in final analyses if he or she had at least 40% of trials included in the analyses. An average of 6.04 HAI+SOC trials and 6.00 LAI+SOC trials were included per participant. Number of trials included did not differ between array types ($t(23) = .096$, $p = .925$).

Analysis of between-group differences

A multivariate analysis of variance (MANOVA) was conducted to assess group differences across the three previously described measures of social attention: prioritization, preference, and detail orientation. The multivariate omnibus F statistic for effect of diagnostic group was also not significant ($F(8,12) = .467$, $p = .857$). This indicates that no group differences were observed for overall mean values for any of the social attention variables.

Analysis of within-group differences

Paired samples t-tests revealed that within the TD group, there was no change in social attention across array type for social preference ($t(10) = 1.84$, $p = .096$), social prioritization ($t(10) = -.749$, $p = .471$), or social detail orientation ($t(10) = .941$, $p = .369$). This indicates that for young typically developing children, social attention was robust, regardless of the context in which it was presented. Paired samples t-tests for participants in the ASD group revealed significant changes in social attention across array type for social preference ($t(10) = 2.619$, $p = .026$) and social detail orientation ($t(10) = 3.734$, $p = .004$), but not for social prioritization ($t(10) = -1.818$, $p = .099$). These data indicate that participants with ASD spent significantly less time looking at faces and made significantly fewer fixations to faces, when paired with HAI images, compared to LAI images. Context, however, did not influence how quickly participants with ASD looked to faces. Mean differences are reflected in Figure 5.5.

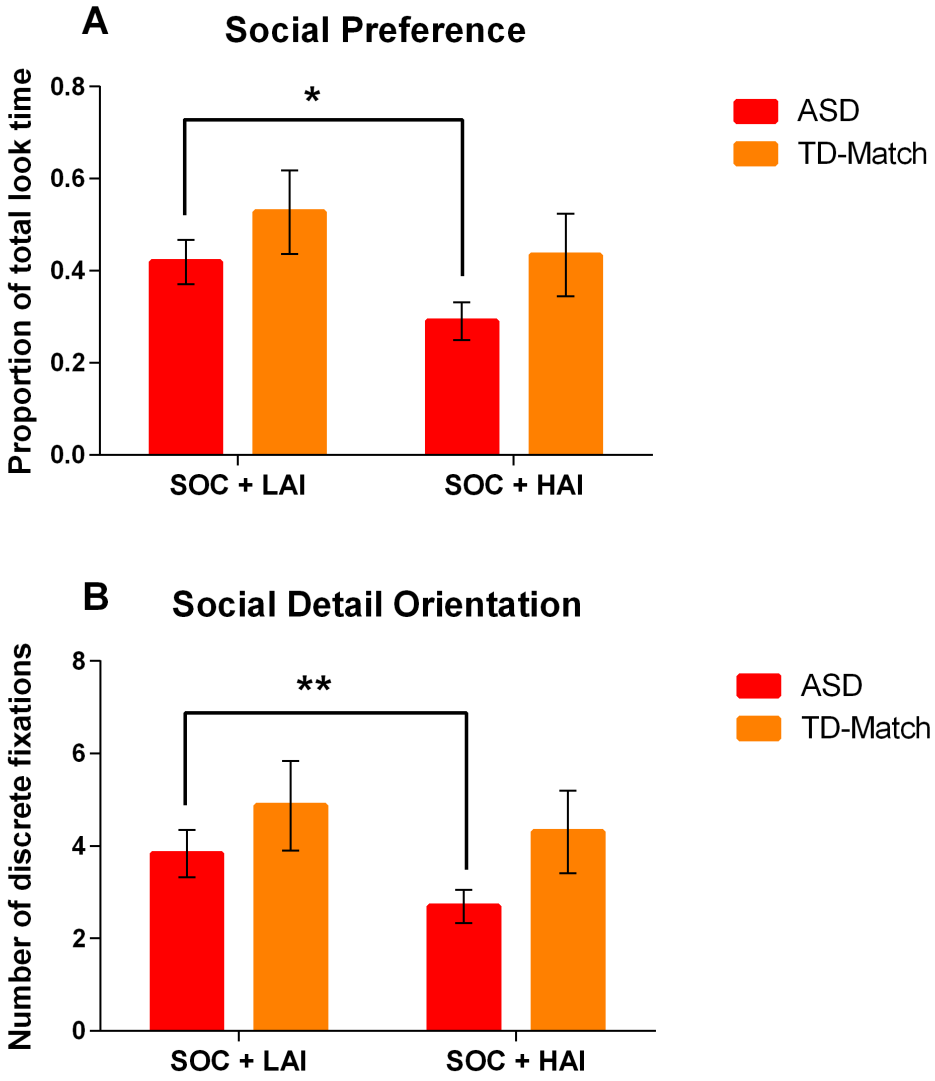

Figure 5.5 **Social attention is context-dependent in early ASD but not TD. (A)** Social preference is decreased in ASD, but not TD-Matched participants, when social images are paired with HAI stimuli. **(B)** Social detail orientation is decreased in ASD, but not TD-Matched participants, when social images are paired with HAI stimuli. Error bars indicate standard error of the mean. *, $p < .05$; **, $p < .01$; *ASD,* Autism Spectrum Disorder; *TD*-Match, typically developing participants matched on developmental-level to ASD; *SOC*, social; *LAI*, low autism interest; *HAI*, high autism interest

Discussion

The purpose of this study was to address the application of a previously establish preferential viewing paradigm for use in young children. This study had two primary: first, to assess feasibility and age-related changes across typical development, and second, to assess feasibility and between- and within-group changes for a sample of individuals with ASD and developmental level-matched peers. High levels of feasibility were established across participant group and diagnostic category; importantly, data inclusion did not differ across array type. Cross-sectional analyses revealed significant age-related changes in social attention, with older participants showing decreased social attention compared to younger participants across both genders. Participants with ASD showed significant changes in social attention between array types, while developmental age-matched typically developing peers maintained social attention across array types.

Regarding Aim 1, it was hypothesized that children with typical development would show a decrease in social attention across both array types, based on previous knowledge about social versus novel object attention in typical development (Libertus & Needham, 2014). This hypothesis was confirmed for all analyzed variables of social attention: preference, prioritization, and detail orientation. However, this age effect was only observed for SOC+HAI arrays. For the purpose of this task, social preference was defined as the proportion of total image viewing time the participant spent viewing social images; therefore, a decrease in social attention is directly proportional to an increase in object attention. Results of preference analysis, therefore, suggest that in typical development, specific types of nonsocial information become increasingly rewarding or preferred over time, while other types of nonsocial information remain constant in

level of arousal or valence. It is important to note that half of the nonsocial stimuli included in our preferential viewing task were labeled as high autism interest and are associated with commonly reported circumscribed interests, they are certainly not items that are solely interesting to individuals with a diagnosis of ASD. Indeed, previous studies have shown increased attention to these items such as these (e.g., trains and vehicles) in comparison to similar neutral items (e.g., plants) in typical development as well as ASD (Thorup, Kleberg, & Falck-Ytter, 2016). However, the results of this study suggest that these items may not become highly rewarding for typically developing children (as indicated by their ability to influence social attention) until later in early childhood.

One potential concern regarding the stimuli in this task is the overlap between HAI items and those that may be more commonly preferred by typically developing males, compared to females. Object category for this task was determined based on a previous study that compared ratings of arousal and valence for each image (Sasson et al., 2012). HAI versus LAI distinctions were made based on high versus low valence ratings by individuals with ASD. Many HAI items were also rated high in valence by typically developing males; however, this pattern was not seen for females with typical development. Therefore, one potential factor influencing the pattern of results seen in typical development is gender rather than age. Indeed, parents of several individuals endorsed an item related to images included in the HAI set as their child's primary interest (e.g., Legos, cars, trains, busses). For this reason, the typically developing sample was recruited to include an equal number of male and female participants. Importantly, analyses indicated that age-dependent effects in this sample were not influenced by gender.

Analyses in Aim 2 next sought to compare toddlers with ASD to a sample of developmental-level matched typically developing peers. Hypotheses for this aim were confirmed. Diagnostic groups differed in patterns social attention, such that individuals with ASD showed context-dependent decreases in social attention, as indexed by decreased preference and detail orientation to social images during SOC+HAI pairings, while TD infants maintained social attention across array types. This is an important extension of our earlier work with this paradigm in adolescents with ASD, as it shows that there is evidence for a significant nonsocial bias that can influence social orientation and attention present in toddlers as young as 29 months of age. Typically developing patterns of attention in this aim are in line with previous findings of increased attention capture by faces (Di Giorgio, Turati, Altoe, & Simion, 2012; Gliga, Elsabbagh, Andravizou, & Johnson, 2009) and increased preference for faces over other highly salient images (Durand, Baudouin, Lewkowicz, Goubet, & Schaal, 2013; Libertus & Needham, 2011). Early life is a time of rich social development, importantly including heavy periods of language development. It is well known that social attention is a critical skill in the development of language skills and that this lack of social attention early in life is hypothesized to contribute to the delayed and / or deficient language development and impaired communicative skills that are diagnostic of ASD (Mundy & Newell, 2007). Therefore, a task that is sensitive to more nuanced differences in social attention may be particularly advantageous for studying ASD in early life.

A primary benefit of eye-tracking technology is the ability to include a wide variety of age groups and levels of functional ability, due to the low task demands placed on participants. Therefore, eye-tracking may be particularly well suited as a tool for early detection of ASD. Currently ASD cannot be diagnosed reliably until around 18 months of age, but is often not

detected until much later in life (Christensen, 2016); however, early detection is a key component in delivery of early intervention, which is a significant predictor of future outcome (Dawson, 2008). Previous studies have already begun to explore the predictive ability of a variety of eye-tracking tasks for future diagnosis (e.g., Chawarska, Macari, & Shic, 2013; Elsabbagh et al., 2012). The preferential viewing task may contribute unique information to such literature, in that it allows for measurement of context-dependent social attention, and the potential influence of highly rewarding nonsocial sources of stimulation, rather than just social attention within a social scene. Importantly, this study established robust social attention in typically developing 12-24 month old children, suggesting that this task may allow for significant differentiation from children who will go onto receive a diagnosis of ASD. Thus a potential next step for future studies may be to include children at risk for ASD, either due to sibling diagnosis or due to parent or pediatrician concern.

Limitations of the current studies are particularly helpful in the design of future studies. First, age-trend analyses should be interpreted with caution, as the study design was cross-sectional rather than longitudinal in nature. Conclusions should only be drawn about the pattern seen across development, rather than regarding the causal mechanisms of social attention throughout experience. Second, these analyses did not address the relationship between aspects of cognitive development and social attention, which may play just as large of a role as typical chronological age development. ASD analyses were primarily limited by a sample size. For the purpose of this study, developmental level was assessed using a composite score from the ABAS, primarily because of difficulty administering measures of cognitive development (e.g., Mullen Scales of Early Development) to children with ASD. However, these analyses warrant future research that

considers both more rigorous measures of cognitive development as well as measures of language and communicative abilities. The latter may begin to contribute to an understanding of the mechanism behind social attentional differences between children with ASD and developmental-level matched peers.

This current study builds upon previous work (Chapter 2) that indicated a potential context-dependent bias in social attention in adolescents with ASD. Over the course of time, this bias could have profound effects on experience-dependent development. The current study begins to address the potential for developmental effects in context-dependent social attention by establishing patterns in typical development and the effects of both developmental and chronological age-related differences. Taken together, these studies demonstrate the ability of this task to capture dynamic changes in social and nonsocial attention across early childhood and differentiate between diagnostic category in the context-dependent modulation of social attention.

REFERENCES

Chawarska, K., Macari, S., & Shic, F. (2013). Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. *Biological Psychiatry*, *74*(3), 195–203.

Christensen, D. L. (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR. Surveillance Summaries*, *65*. https://doi.org/10.15585/mmwr.ss6503a1

Colombo, J., Mitchell, D. W., & Horowitz, F. D. (1988). Infant Visual Attention in the Paired-Comparison Paradigm: Test-Retest and Attention-Performance Relations. *Child Development*, *59*(5), 1198–1210. https://doi.org/10.2307/1130483

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., … Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, *8*(4), 519–526.

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, *20*(03), 775–803.

Elison, J. T., Sasson, N. J., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2012). Age trends in visual exploration of social and nonsocial information in children with autism. *Research in Autism Spectrum Disorders*, *6*(2), 842–851.

Elsabbagh, M., Mercure, E., Hudry, K., Chandler, S., Pasco, G., Charman, T., … others. (2012). Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Current Biology*, *22*(4), 338–342.

Goren, C. C., Sarty, M., & Wu, P. Y. K. (1975). Visual Following and Pattern Discrimination of Face-like Stimuli by Newborn Infants. *Pediatrics*, *56*(4), 544–549.

Harrison, P., & Oakland, T. (2003). Adaptive behavior assessment system (ABAS-II). *San Antonio, TX: The Psychological Corporation*. Retrieved from http://69.164.214.107/downloads/compendium_instruments_publishers.pdf

Johnson, M. H., Dziurawiec, S., Ellis, H., & Morton, J. (1991). Newborns' preferential tracking of face-like stimuli and its subsequent decline. *Cognition*, *40*(1), 1–19.

Kelly, D. J., Liu, S., Ge, L., Quinn, P. C., Slater, A. M., Lee, K., … Pascalis, O. (2007). Cross-Race Preferences for Same-Race Faces Extend Beyond the African Versus Caucasian Contrast in 3-Month-Old Infants. *Infancy : The Official Journal of the International Society on Infant Studies*, *11*(1), 87. https://doi.org/10.1080/15250000709336871

Kelly, D. J., Quinn, P. C., Slater, A. M., Lee, K., Gibson, A., Smith, M., … Pascalis, O. (2005). Three-month-olds, but not newborns, prefer own-race faces. *Developmental Science*, *8*(6), F31–F36.

Libertus, K., & Needham, A. (2014). Face preference in infancy and its relation to motor activity. *International Journal of Behavioral Development*, *38*(6), 529–538.

Merin, N., Young, G. S., Ozonoff, S., & Rogers, S. J. (2007). Visual fixation patterns during reciprocal social interaction distinguish a subgroup of 6-month-old infants at-risk for autism from comparison infants. *Journal of Autism and Developmental Disorders*, *37*(1), 108–121.

Mundy, P., & Newell, L. (2007). Attention, Joint Attention, and Social Cognition. *Current Directions in Psychological Science*, *16*(5), 269. https://doi.org/10.1111/j.1467-8721.2007.00518.x

Pascalis, O., de Schonen, S., Morton, J., Deruelle, C., & Fabre-Grenet, M. (1995). Mother's face recognition by neonates: A replication and an extension. *Infant Behavior and Development*, *18*(1), 79–85.

Robins, D. L., Fein, D., & Barton, M. L. (1999). Modified checklist for autism in toddlers (M-CHAT) follow-up interview. *Self-Published*. Retrieved from http://www.mainequalitycounts.org/image_upload/mCHAT2%20followup%20questions.pdf

Rose, S. A., Gottfried, A. W., Melloy-Carminar, P., & Bridger, W. H. (1982). Familiarity and novelty preferences in infant recognition memory: Implications for information processing. *Developmental Psychology*, *18*(5), 704–713. https://doi.org/10.1037/0012-1649.18.5.704

Sasson, N. J., Dichter, G. S., & Bodfish, J. W. (2012). Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PloS One*, *7*(8), e42457.

Sasson, N. J., & Touchstone, E. W. (2014). Visual attention to competing social and object images by preschool children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 584–592.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive Behavior Profiles in Asperger Syndrome and High-Functioning Autism. *Journal of Autism & Developmental Disorders*, *35*(2), 145–158.

Thorup, E., Kleberg, J. L., & Falck-Ytter, T. (2016). Gaze Following in Children with Autism: Do High Interest Objects Boost Performance? *Journal of Autism and Developmental Disorders*, 1–10.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249.

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W. (2016). Social Orienting and Attention Is Influenced by the Presence of Competing Nonsocial Information in Adolescents with Autism. *Frontiers in Neuroscience*, *10*.

Valenza, E., Simion, F., Cassia, V. M., & Umiltà, C. (1996). Face preference at birth. *Journal of Experimental Psychology: Human Perception and Performance*, *22*(4), 892–903. https://doi.org/10.1037/0096-1523.22.4.892

CHAPTER 6

VISUAL ATTENTION TO AFFECTIVE INFORMATION DOES NOT DIFFER BETWEEN ADULTS WITH AUTISM AND THOSE WITH DEPRESSION AND MAY BE RELATED TO OVERLAPPING MECHANISMS OF REPETITIVE THINKING

Introduction

The majority of individuals with autism spectrum disorder (ASD) meet criteria for at least one co-occurring psychiatric condition (Mattila et al., 2010; Mazefsky et al., 2012; Simonoff et al., 2008). Depression is among the most prevalent of these comorbid diagnoses (Buck et al., 2014; Simonoff et al., 2008). Individuals with ASD are diagnosed with depression at increased rates from the typically developing population (Kerns et al., 2016) and tend to report high levels of depressive symptoms, even in individuals who do not meet clinical criteria for depression diagnoses (Gotham, Bishop, Brunwasser, & Lord, 2014; Gotham, Unruh, & Lord, 2015). Reports of increased incidence of depression, coupled with overlap between autistic and depressive symptomology, has opened the door to an emerging literature exploring mechanisms that may be common to both disorders.

The presence of depression in ASD is intuitive from both psychosocial and biological standpoints. In addition to diagnostic criteria that include difficulty in general social and communicative abilities, individuals with ASD may specifically show impairment in navigation and maintenance of reciprocal social relationships (Howlin, Goode, Hutton, & Rutter, 2004; Lord et al., 2000). Such challenges likely leave these individuals particularly susceptible to

loneliness and lack of social connectedness, both of which are reported at increased incidence in ASD (Bauminger & Kasari, 2000; White & Roberson-Nay, 2009; Lasgaard et al., 2010) and predicting factors of depression in typically developing populations (Williams & Galliher, 2006; Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006). Therefore, the presence of one psychiatric disorder may increase environmental risk factors for development of a second. This may be particularly salient when considering instances of negative interactions with, or feedback from, peers (Mazefsky et al., 2012). Coupled with these psychosocial risk factors are high rates of familial mood disorders, implicating potentially increased genetic risk for psychiatric comorbidities in individuals with ASD (DeLong, 2004; Bolton, Pickles, Murphy, & Rutter, 1998; Piven & Palmer, 1999). Therefore, individuals with ASD may receive a "double hit" in psychiatric susceptibility.

A study by Gotham and colleagues sought to identify mechanisms by which psychosocial factors may influence the development of depression in verbally fluent adults with ASD (Gotham et al., 2014). In line with the above outlined hypotheses, individuals who perceived greater individual impairment due to autistic symptomology exhibited higher levels of depression. However, this relationship was not true of all individuals with ASD. Rather, this association between psychosocial vulnerability and depression severity was only present in individuals who displayed high levels of rumination. Therefore, rumination may be a moderating factor in the intersection between autism and depression.

Rumination is implicated in both the onset and maintenance of depression (Nolen-Hoeksema, 2000). This passive and repetitive pattern of thought has also been shown to perpetuate

depressed mood and therefore prolong and / or increase the severity of episodes of depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Repetitive thought patterns, however, are not specific to depression. Rather, this form of repetitive behavior may be observed across a range of psychiatric diagnoses, including OCD (Van Oppen, Hoekstra, & Emmelkamp, 1995) and anxiety (Nolen-Hoeksema, 2000). Perseverative thinking is also evident in the core features of autism, including insistence on sameness, which has been shown to be related to rumination (Gotham et al., 2013). Patterns of repetitive thinking may also manifest as *positive* patterns of thought in ASD, in the context of circumscribed interests. Therefore, individuals with ASD may be particularly susceptible to experiencing or engaging in cognitive patterns that are characteristic of depression.

In the context of depression, rumination has been found to be associated with biased processing of negative emotional information (Duque & Vázquez, 2015; Joormann, Dkane, & Gotlib, 2006). Specifically, negative information has been shown to alter performance during attentional tasks, such that attention is biased toward negative information and away from task-relevant cues (e.g., Donaldson, Lam, & Mathews, 2007; Duque & Vázquez, 2015; Gotlib et al., 2004; Gotlib & Cane, 1987; Segal, Gemar, Truchon, Guirguis, & Horowitz, 1995). One method for assessing negative biases in rumination is a paired viewing paradigm, where attentional orienting and attention maintenance is measured by pairing an emotional face with an identical face of neutral valence. In the only study of its kind, this paradigm was used to demonstrate attentional differences to depression-specific stimuli, such that individuals in this group displayed longer initial fixation duration and longer total fixation duration to sad images, compared to healthy controls (Duque & Vázquez, 2015). Further, increased attention to sad faces was significantly

correlated with the severity of depressive symptoms.

The current study had two aims. First, I sought to assess emotional bias in individuals with ASD, compared to individuals with major depressive disorder (DEP) and healthy controls (TD). Specifically, I hypothesized that individuals with ASD would display patterns of attention more similar to participants with DEP, reflected as increased attention to sad images and decreased attention to happy images, compared to TD participants. Second, I sought to assess the relationship between ASD-specific repetitive patterns and depressive symptomology, in individuals with ASD. I hypothesized that individuals with ASD who exhibit more intensity in patterns of repetitive behavior would also demonstrate more severe rumination and depression.

Methods

Participants

Three diagnostic cohorts were recruited for this study: Those with an autism spectrum disorder (ASD; N = 29), typically developing adults with a current depressive disorder (DEP-C; N = 24), and typically developing adults with no history of anxiety, depression, or family history of ASD (TD; N = 24). Participants were recruited from national and local (mid-South) resources. Eligibility criteria included verbal IQ>=80; verbal fluency per Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2; Lord et al., 2012) module selection criteria; reading level >= 5th grade; 20/20 vision at 80 cm on the Snellen eye chart; and no history or concerns of psychotic or bipolar disorders, current substance use disorders, or uncorrected vision problems or ocular abnormalities. Participants in the clinical cohorts had previous diagnoses of ASD or depressive disorder, respectively. Table 6.1 provides demographic information by cohort.

Table 6.1 *Demographics and Participant Characterization for Study 5*

Characteristic	ASD (N = 29)	DEP-C (N = 24)	TD (N = 24)
Age (years)	22.8 (4.1)	25.3 (4.7)	25.4 (5.0)
Gender	24 M / 5 F	15 M / 9 F	12 M / 12 F
Full Scale IQ	103.2 (12.3)	109.7 (10.3)	111.9 (14.0)
Social Responsiveness Scale			
T-Score	67.3 (10.6)	54.6 (8.8)	42.8 (4.2)
Ruminative Response Scale			
Total Score	45.1 (13.4)	54.8 (7.4)	31.8 (7.7)
Beck Depression Inventory			
Total Score	13.3 (9.4)	26.9 (7.1)	2.8 (2.3)
Interest Scale			
Total Severity	12.0 (3.5)	9.7 (2.2)	8.0 (1.7)
Autism Diagnostic Observation Schedule			
Social + Communication	6.7 (2.0)	--	--
Stereotyped Behavior + Restricted Interest	6.2 (2.8)	--	--
Total Severity	6.4 (2.2)	--	--

ASD, Autism Spectrum Disorder; *DEP*-C Depression; TD; typically developing; *M*, male; *F*; female

Procedures included a telephone screening, followed by 1-2 data collection lab visits, in which the current task was one in a larger study. The ADOS-2 was administered to all participants in the ASD cohort to confirm diagnosis, as well as to any participants who exceeded clinical cut-offs on the Social Responsiveness Scale (SRS-2; Constantino & Gruber, 2002) or Autism Spectrum Quotient (AQ; (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). The Structured Clinical Interview for DSM Disorders (SCID-5; First, Gibbon, Spitzer, Benjamin, & Williams, 1997) depression module and the Mini International Neuropsychiatric Interview (MINI 5.0; Lecrubier et al., 1997) were administered to all participants to confirm diagnosis and/or assess emotional health history.

Stimuli and task

Affective Preference Task

The preferential viewing task used for this study is comprised of paired arrays containing both an emotional and neutral facial expression made by the same person. Arrays were characterized by the presence of either a sad or happy face, with 28 arrays per condition. Arrays were balanced by gender (14 males and 14 females per condition) and laterality of emotional image (right vs. left balanced). Face images were modified from the Karolinska Directed Emotional Faces (KDEF) database (Lundqvist, Flykt, & Öhman, 1998), by using an oval window frame to remove salient aspects such as hair. Emotional intensity for these images has been validated in previous studies (Schaefer, Nils, Sanchez, & Philippot, 2010). Images were presented in grayscale to better account for low-level stimulus properties, and further modified using Adobe Photoshop software to balance luminosity. This task has been previously described by its developers, Duque and colleagues (Duque & Vázquez, 2015). Refer to Figure 6.1 for task schematic.

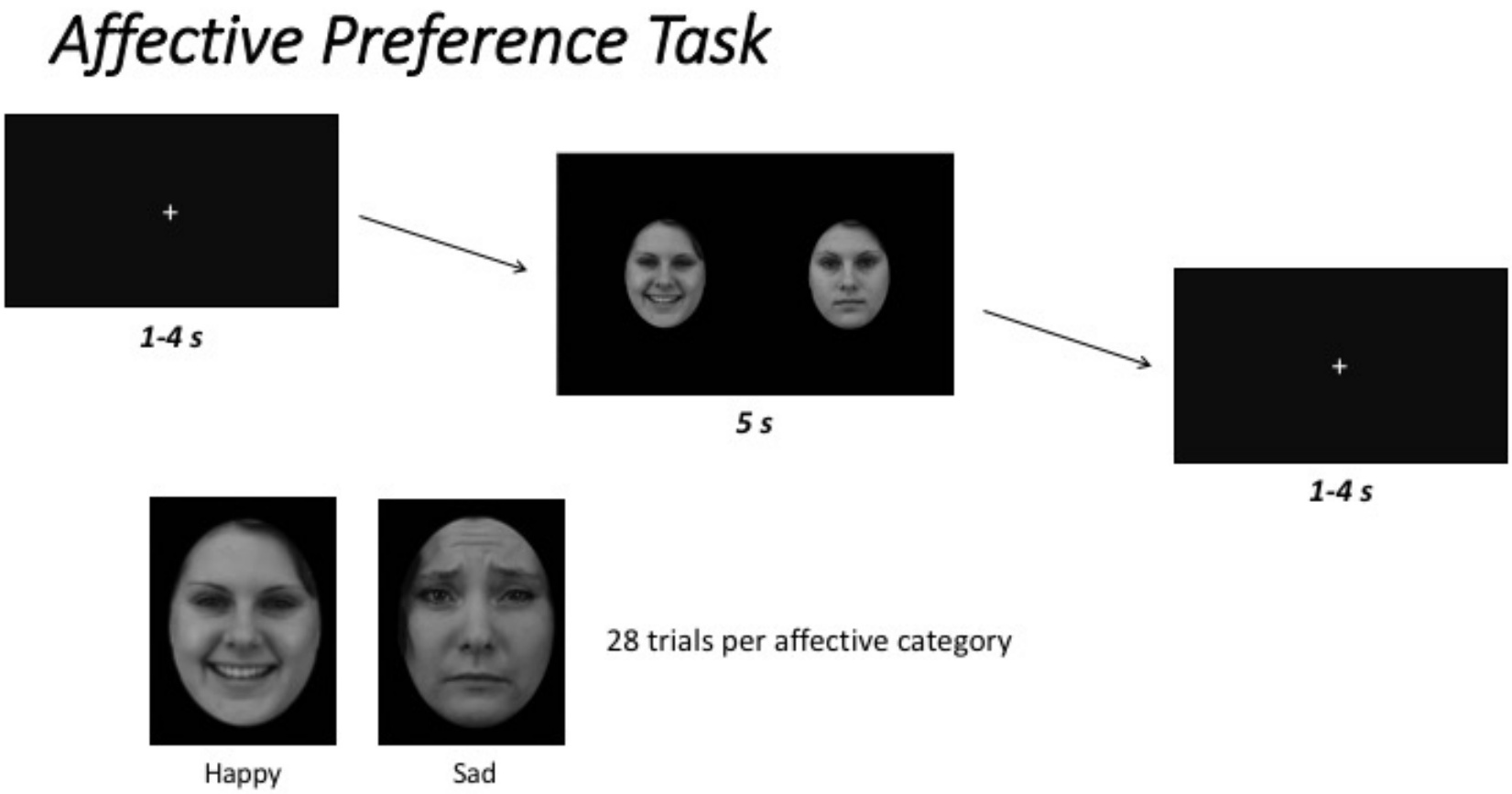

Figure 6.1 **Schematic of the affective preference task.**

Eye-tracking procedure

Testing occurred in a research laboratory. Participants sat approximately 60 cm from a 1,024 horizontal x 768 vertical 17-inch display and viewed stimuli subtending a visual angle of 16.1 degrees. Eye movements were recorded with a Tobii X2-60 eye tracker (Tobii Technology, Stockholm, Sweden). The system uses an infrared light to produce reflection patterns on the corneas of the eye and monitors these reflections relative to the eye's position. This system samples at a rate of 60 Hz. This eye tracking system is mounted on the computer monitor, and therefore does not interfere with data collection. The system allows for head movement within a cubic space of 30x15x20 cm from a distance of 60 cm, allowing the participants to view in a naturalistic manner.

The passive viewing task was comprised of 56 trials (28 images per category), with affective category randomized across trials. Each trial began with a presentation of a white fixation cross in the center of the screen, displayed at a variable duration of 1-4 seconds followed by the presentation of an affective array for 5 seconds. Participants were instructed to view the faces naturally, but given no further instructions.

Self-report measures

Beck Depression Inventory

The Beck Depression Inventory (BDI; Beck, et al., 1996) is a widely used scale of depression severity for adolescents and adults. This self-report measure is designed to capture depression-related emotions, physical and psycho-somatic symptoms, and lifestyle changes. This measure

has been found to have high internal consistency and strong convergent validity (Dozois, Dobson, & Ahnberg, 1998).

Ruminative Response Scale

The Ruminative Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991) is a frequently used measure of self- and symptom-focused thoughts that may persist as patterns of rumination, including brooding and reflective pondering. This scale was developed to assess rumination that is related to, but not confounded by depression (Treynor, Gonzalez, & Nolen-Hoeksema, 2003).

Interest Scale

The Interest Scale (Turner-Brown et al., 2011) is used to collect detailed information on the presence and severity of circumscribed interests. The severity score characterizes an individual's strongest interest, including the degree to which this interest is shared with other people (social involvement), and the flexibility, frequency, intensity, interference, and accommodation of that specific interest.

Analysis of task performance

The nature of the paired preference task requires that each participant is looking at the slide for a sufficient amount of time to observe both images. Therefore, I developed a method to exclude participants based on insufficient total look time per slide, as to eliminate potential bias from the data. Total viewing time was calculated for each trial; any trial with less than 70% total viewing time (3.5 seconds) was excluded from analyses. Further, any participant with fewer than 60% of trials included, per condition, was excluded from group means due to insufficient data. Applying

these criteria resulted in exclusion of 2 participants with typical development, 8 participants with ASD, and 2 participants with depression. Analyses revealed that the excluded group did not differ from the included participants on IQ (t = -.094, p = .926), age (t = -.672, p = .532), autism severity (ADOS; t = .486, p = .643) or depression severity (BDI; t = .361, p = .719).

Eye-tracking variables

Gaze patterns were analyzed as a result of conducting fixation analyses. Fixations were classified using the Tobii Studio I-VT filter, which defines fixations as gaze moving at a velocity slower than 30 degrees per second, for at least 60 milliseconds. Three dependent variables were extracted from the data collected: (a) Prioritization: the latency to first fixate on each stimulus type, which measures attention capture and orienting; (b) Attention delay: The initial duration of image exploration, which measures stimulus disengagement; and (c) Preference: the proportion of on screen fixation time devoted to each image type, relative to total time spent on the stimulus array.

Statistical analysis

Repeated measures analysis of variance (RM-ANOVA) was conducted on each of the primary variables, with emotion type (neutral, sad, happy) as the within-subjects variable and group (ASD, DEP-C, TD) as the between groups variable. Post-hoc univariate ANOVA analyses were also performed to assess single condition between group differences, as well as paired samples t-tests to determine within-subjects differences.

A second set of analyses was performed on participants with ASD only, who were grouped by median split on the overall severity score from the Interest Scale (IS). Analogous RM-ANOVAs were performed to compare between emotions (sad, happy) for participants in high-IS, low-IS, and DEP-C groups.

Results

Aim 1: Cross-diagnostic gaze patterns

Prioritization: Sad

A 2 (emotion: sad, neutral) x 3 (group: TD, ASD, DEP-C) RM-ANOVA was conducted to determine whether participants differed in latency to sad versus neutral faces. Group means are displayed in Figure 6.2a. There was no emotion x group interaction ($F(2, 62)= 1.07$, $p = .348$). There was no main effect of group ($F(1, 62) = .703$, $p = .499$). There was a main effect of emotion ($F(1, 62) = 20.398$, $p < .001$), indicating that across groups, participants were faster to fixate on sad faces than neutral faces. Follow-up paired-samples t-tests revealed that this effect was driven by participants in the ASD group, who displayed significantly faster fixations to sad than neutral faces ($t = -3.960$, $p = .001$), while this effect only reached trend-significance in TD ($t = -1.981$, $p = .061$) and DEP-C participants ($t = -1.972$, $p = .062$).

Prioritization: Happy

A 2 (emotion: happy, neutral) x 3 (group: TD, ASD, DEP-C) RM-ANOVA was conducted to determine whether participants differed in latency to happy versus neutral faces. Group means are displayed in Figure 6.2b. There was no emotion x group interaction ($F(2, 62)= 2.218$, $p = .117$). There was no main effect of group ($F(1, 62) = 1.582$, $p = .214$). There was a main effect of

emotion ($F(1, 62) = 22.714$, $p < .001$), indicating that across groups, participants were faster to fixate on happy faces than neutral faces. Follow-up paired-samples t-tests revealed participants with ASD did not display an orienting effect toward happy faces ($t = -1.39$, $p = .180$). Rather, this effect was driven by participants in the TD group, who displayed significantly faster fixations to happy than neutral faces ($t = -7.332$, $p < .001$), while participants with DEP-C demonstrated a bias toward happy faces only at trend significance ($t = -1.941$, $p = .066$). Follow-up ANOVA further revealed that orienting toward happy faces was delayed in participants with DEP-C compared to TD ($F(1, 62) = 2.26$, $p = .037$).

Prioritization: Sad vs. happy

A 2 (emotion: sad, happy) x 3 (group: TD, ASD, DEP-C) RM-ANOVA was conducted to determine whether participants differed in latency to sad versus happy faces. Group means are displayed in Figure 6.2c. There was a significant emotion x group interaction ($F(2, 62)= 6.016$, $p = .004$). There was no main effect of emotion ($F(1, 62) = 1.018$, $p = .317$) or group ($F(1, 62) = 1.23$, $p = .216$). Follow-up ANOVA revealed that this significant interaction was driven by mean differences in the TD group, who displayed faster latencies to happy faces than to sad ($t = 3.554$, $p = .002$), while ASD ($t = -1.073$, $p = .296$) and DEP-C ($t = -.400$, $p = .694$) participants did not.

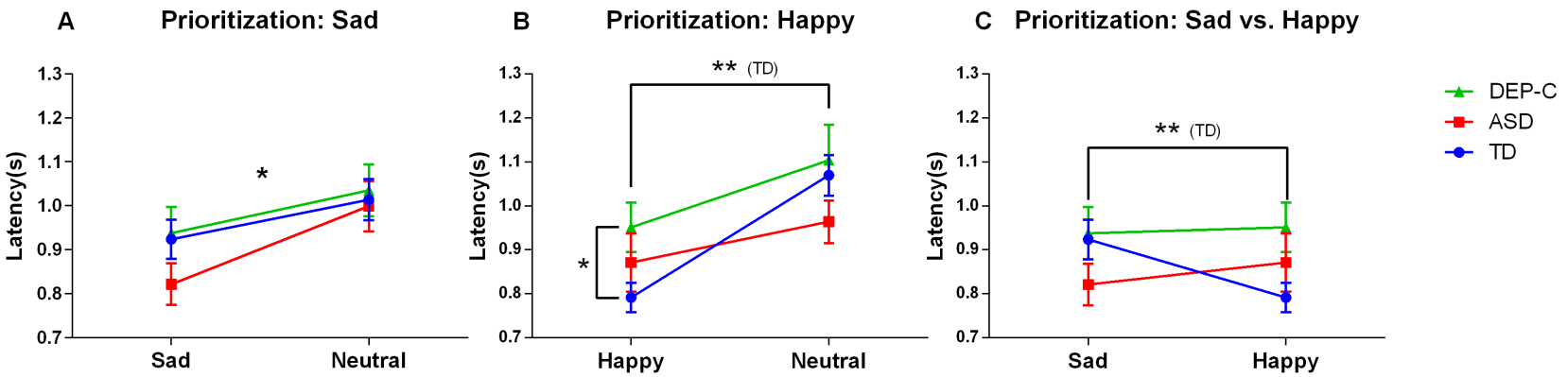

Figure 6.2 **Prioritization of affective stimuli for participants with TD, ASD, and DEP-C. (A)** Participants across groups prioritize sad faces over neutral. **(B)** Participants with TD demonstrate prioritization of happy faces and increased effects, compared to DEP-C. **(C)** Participants with TD are quicker to look to happy, compared to sad, faces. Error bars indicate standard error of the mean. *, $p <$ .05; **, $p <$ .01; *ASD,* Autism Spectrum Disorder; *TD*, typically developing; *DEP-C*, depression.

Attention delay: Sad vs. happy

A 2 (emotion: sad, happy) x 3 (group: TD, ASD, DEP-C) RM-ANOVA was conducted to determine whether participants differed in duration of stimulus disengagement between emotional stimuli. Group means are displayed in Figure 6.3. There was a no emotion x group interaction ($F(2, 62)= 1.658$, $p = .199$). There was no main effect of emotion ($F(1, 62) = .205$ $p = .652$) or group ($F(1, 62) = .186$, $p = .831$). Follow-up paired samples t-tests revealed no significant changes in attention delay within groups, although TD participants did approach significance ($t = -1.841$, $p = .080$), showing a pattern of increased attention delay for happy images, compared to sad.

Preference: Sad vs. happy

A 2 (emotion: sad, happy) x 3 (group: TD, ASD, DEP-C) RM-ANOVA was conducted to determine whether participants differed in overall attention to emotional stimuli. Group means are displayed in Figure 6.4. There was a significant emotion x group interaction ($F(2, 62)= 9.330$, $p < .001$). There was a main effect of emotion ($F(1, 62) = 4.774$, $p = .033$) and group ($F(1, 62) = 6.680$, $p = .002$). Follow-up ANOVA revealed that this significant interaction was driven by mean differences in the TD group, who displayed increased preference for happy faces, compared to ASD and DEP-C groups ($F(1, 62) = 16.103$, $p < .001$).

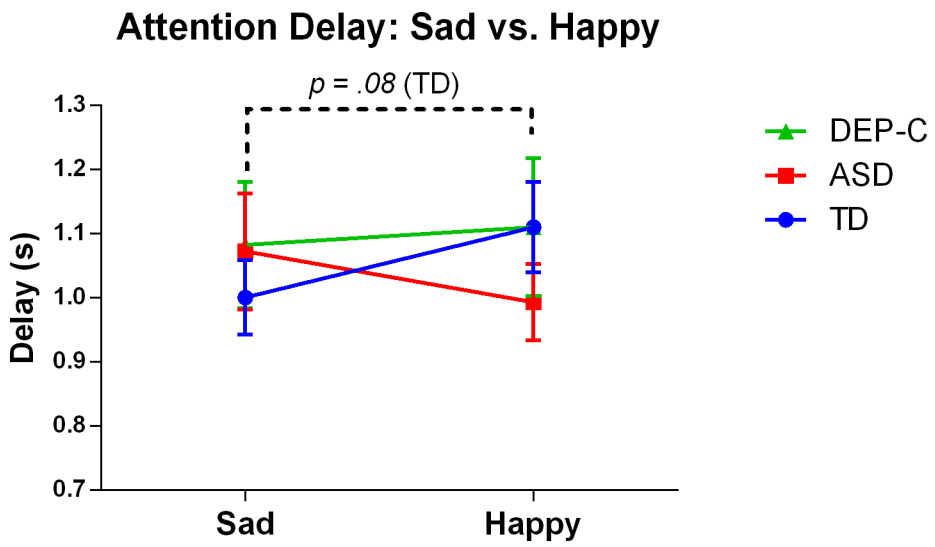

Figure 6.3 **Attention delay to affective stimuli for participants with TD, ASD, and DEP-C.** Error bars indicate standard error of the mean. *ASD,* Autism Spectrum Disorder; *TD*, typically developing; *DEP-C*, depression.

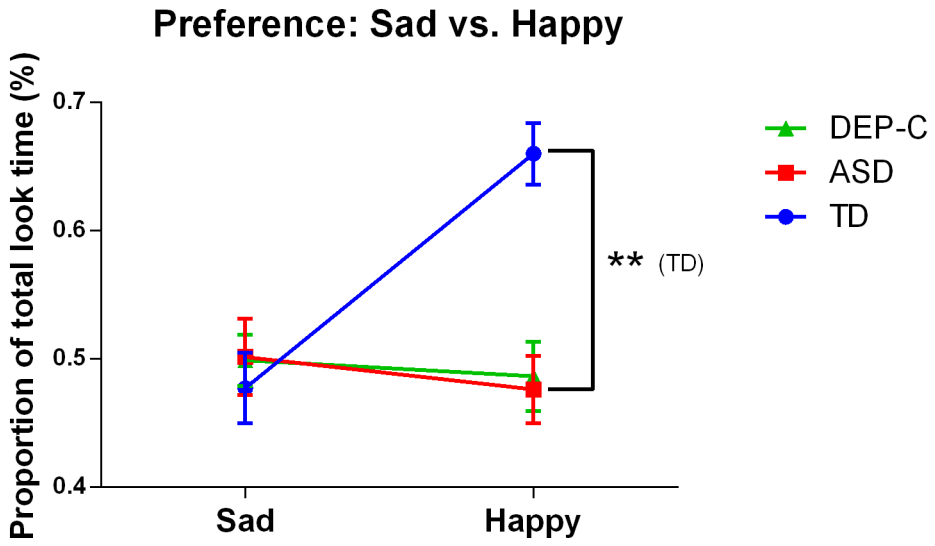

Figure 6.4 **Preference for affective stimuli for participants with TD, ASD, and DEP-C.** Error bars indicate standard error of the mean. **, $p < .01$; *ASD,* Autism Spectrum Disorder; *TD*, typically developing; *DEP-C*, depression.

Aim 2: Patterns of repetitive behavior and thought in ASD

The next set of analyses focused on participants with ASD. Participants were grouped, using a median split, by scores on the Interest Scale (IS), which assesses intensity of an individual's primary circumscribed interest. Participants with high IS severity scores had significantly higher scores of rumination (RRS; $F(1, 24) = 6.587$, $p = .017$) and depression (BDI; $F(1, 24) = 5.851$; $p = .024$) than participants with low IS severity scores. To determine whether these group differences could be accounted for by autism severity, analyses were repeated, this time controlling for ADOS Overall Severity score. IS-split groups still showed significantly different RRS scores ($F(1, 21) = 4.699$, $p = .042$), however adjusted mean differences for BDI total scores only approached significance $F(1, 21) = 4.046$, $p = .057$). Overall, these analyses suggest that the relationship between intensity of circumscribed interests and symptoms of depression may be attributed to similarities in mechanisms of repetitive behavior and thought, rather than confounded by the aforementioned overlap between ASD and depressive-related social symptomology. Group means are displayed in Figure 6.5.

A second set of analyses was conducted to compare gaze patterns between both ASD IS-split groups and the DEP-C groups. A 2 (emotion: sad, happy) x 3 (group: low-IS, high-IS, DEP-C) RM-ANOVA for preference revealed no group x emotion interaction ($F(2, 37) = .326$, $p = .724$) and no main effect of emotion ($F(1, 37) = .511$, $p = .479$) or group ($F(1, 37) = 2.233$, $p = .121$). However, follow-up ANOVA revealed that participants with high IS spent significantly more time viewing sad faces than participants with low IS ($F(1, 37) = 2.332$, $p = .038$). Participants with DEP-C did not differ from either group (all ps > .05). Group means are displayed in Figure

6.6. Additional RM-ANOVAs for latency and attention delay revealed no differences between groups.

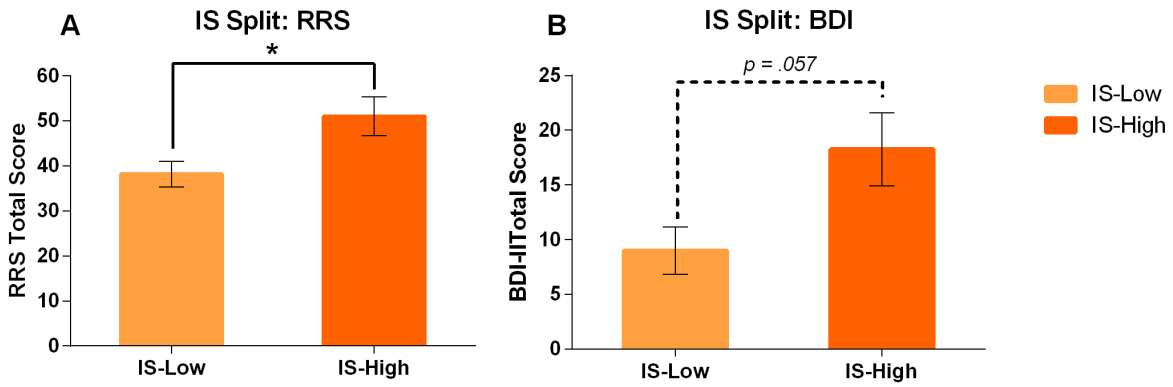

Figure 6.5 **Clinical features of depression vary by severity of circumscribed interest in ASD. (A)** Participants with ASD with high severity of circumscribed interests show increased rumination, compared to participants with ASD with low severity circumscribed interests. **(B)** Participants with ASD with high severity of circumscribed interests show increased scores of clinical depression, compared to participants with ASD with low severity circumscribed interests. Error bars indicate standard error of the mean. *, $p < .05$; *IS*, Interest Scale; *RRS*, Ruminative Response Scale; *BDI*, Beck Depression Inventory.

Figure 6.6 **Affective preference varies by circumscribed interest severity in ASD.** Error bars indicate standard error of the mean. *, $p < .05$; *IS*, Interest Scale; *ASD,* Autism Spectrum Disorder; *DEP-C*, depression.

Discussion

The purpose of the current study was to assess attentional indices of depression in participants with ASD. Visual attention was measured using a preferential viewing task, which paired emotional and neutral faces in order to assess a variety of indices of bias toward valenced (sad and happy) stimuli. Participants in this study included individuals with ASD with average IQ, individuals with current depression, and never-depressed, typically developing controls. A second set of analyses examined the relationship between several aspects of repetitive thinking and behavior in participants with ASD, using both depression-specific and autism-specific questionnaires.

The first aim of the study was to characterize visual attention to emotional faces across diagnostic groups. I hypothesized that that participants with ASD would show patterns of visual attention more similar to participants with current diagnoses of clinical depression, rather than never-depressed controls. Specifically, I predicted that ASD and DEP-C groups would show increased attention to sad faces and decreased attention to happy faces. The overall pattern of results confirmed the general hypothesis by revealing that participants with ASD display visual attention that is much more similar to participants with depression than TD controls. However, patterns of attention to sad stimuli did not seem to differentiate between groups. Rather, differences were most pronounced for happy arrays. Participants with DEP-C displayed increased latency to happy faces, compared to TD participants and both groups displayed decreased preference for happy faces, compared to TD participants. These results differ from a previous study using a nearly identical preferential viewing task administered to only TD and DEP-C participants (Duque & Vázquez, 2015). Similar to the current study, Duque and

colleagues found emotional biases for happy versus sad faces, although no between-group differences were observed. Further, participants with depression displayed significantly increased overall viewing time for sad faces, compared to never depressed controls, which was not observed in the current study. Alternatively, Duque and colleagues found only a marginally significant difference in viewing time for happy faces between diagnostic groups, while the current study observed a substantial increase in viewing time for TD participants. Overall, it can be concluded that sad images elicited a more powerful diagnostic effect in the earlier study, while gaze patterns to happy faces were more indicative of diagnostic status in the current study. Notably, these study samples were from different cultures, which has been shown in some contexts to influence differences in emotional attention that may not be detected in emotion labeling or valence ratings (Ko, Lee, Yoon, Kwon, & Mather, 2011).

The overall pattern of results supports the primary hypothesis for aim 1. Participants with ASD demonstrated patterns of emotional bias more similar to that of the DEP-C group than TD controls. Importantly, participants with ASD did not have co-occurring diagnoses of depression and presented with BDI scores significantly lower than the DEP-C group. Therefore, the similarities between these two groups cannot be attributed to diagnostic overlap. To date, no previous studies have compared patterns of emotional bias between autism and depression, although there is a recently established literature characterizing the increased incidence of depressive symptomology in ASD.

The second aim of the study was to evaluate the relationship between autism-specific and depression-related patterns of repetitive thinking in individuals with ASD. The relationship

between repetitive patterns within and outside of ASD has been largely overlooked in the existing literature. This can likely be attributed to differences in the way these repetitive patterns are classified. First, repetitive patterns in depression tend to present as rumination, which is defined as passive repetitive *thought* that focuses on one's own distress (Nolen-Hoeksema & Morrow, 1991). Repetitive patterns in ASD, on the other hand, are most frequently considered and discussed in terms of overt *behavior*, manifesting as stereotypies, insistence on sameness, rituals and compulsions, and restricted interests (Lam & Aman, 2007). Second, repetitive patterns in depression are associated with *negative* valence (i.e. rumination), while repetitive patterns in autism are sometimes thought to be associated with *positive* valence (e.g., circumscribed interests; Turner-Brown, Lam, Holtzclaw, Dichter, & Bodfish, 2011). Indeed, some recent hypotheses regarding the development of depression in autism have suggested that valence discrepancies negate the possibility of shared mechanism between these two repetitive patterns (Burrows, Timpano, & Uddin, 2017). Despite these differences in presentation, the high prevalence of depression in children and adults with ASD warrants further consideration of potential shared mechanisms between the two disorders.

For the purpose of this study, autism-specific repetitive thinking was described as the intensity of an individual's circumscribed interest, rather than a global measure of repetitive behavior. Previous research in ASD has shown that repetitive patterns in ASD are not unitary; rather, they seem to parse into multiple distinct factors (Lam, Bodfish, & Piven, 2008). Further, while most repetitive behaviors observed in ASD are also common to other developmental and neuropsychiatric disorders, circumscribed interests may be pathognomonic to ASD (Turner-Brown et al., 2011). Therefore, measuring circumscribed interests presents an opportunity to

capture variance that may be specific to autism. The severity score used here indexes the frequency of engagement with an individual's primary interest, flexibility associated with the interest, and the amount the interest interferes with functional and adaptive behavior. I hypothesized that individuals with ASD who have more intense circumscribed interests would also show higher levels of rumination and depression. The implications of this hypothesis suggest that individuals with ASD may simply show a greater propensity for repetitive thinking, and that this pattern of repetition can be co-opted by information of both positive and negative valence. An alternative hypothesis is that individuals with high intensity circumscribed interests would show *lower* severity of rumination and depression. The implications of this hypothesis suggest that an increased propensity to engage in positive patterns of repetitive thought may be protective against perseverative negative thought. The data presented here support the first hypothesis, as individuals with ASD who endorsed higher levels of intensity related to circumscribed interests also displayed high levels of rumination and high subclinical depression scores. Importantly, this relationship could not be accounted for by increased autism severity.

Increased incidence of depression in autism suggests the potential for shared neural mechanisms between the two diagnoses. One candidate for these shared neural processes is that of repetitive thinking. Rumination is a pattern of cognition and, therefore, involves coordination between multiple areas of the cortex, including those devoted to introspection and memory, as well as salience detection and executive function (Burrows, Usher, Schwartz, Mundy, & Henderson, 2016). Burrows and colleagues (2016) proposed that repetitive thinking may develop via dysfunctional neural modulation between networks in the brain that underlie these latter two processes, specifically, the default mode network (DMN) and the salience network. Previous

studies in depression have shown variation in functional connectivity between key nodes of these networks: the insula and the anterior cingulate cortex (ACC) (Berman et al., 2014; Connolly et al., 2013), and further, that this variability is related to rumination scores (Kaiser et al., 2015). From this model, it can be hypothesized that rumination comes about through aberrant detection of salient stimuli (e.g., increased salience placed on negative content), coupled with an inability to exert flexible control over such thought patterns. Therefore, a behavioral index of this neural endophenotype may be increased and perseverative attention to depression-related or negative stimuli.

Individuals with autism have also been shown to have alterations in connectivity within the DMN and the salience network (e.g., Hahamy, Behrmann, & Malach, 2015; Kennedy & Courchesne, 2008; Nomi & Uddin, 2015; Uddin et al., 2013), although variation in the connectivity between these two networks has yet to be explicitly tested. However, at least one study has demonstrated that activity in key nodes of the DMN (ACC) and salience network (insula) distinguishes individuals with ASD from peers during engagement with items of circumscribed interest; further, in this study, insular activity was related to circumscribed interest intensity. A recent study of network connectivity in ASD revealed hyper-connectivity in the salience network, which was also related to overall severity of repetitive behavior (Uddin et al., 2013). Increased neural responses in nodes of the DMN (ventromedial prefrontal cortex) and salience network (amygdala, striatum) have also been observed in ASD during viewing of sad faces (Weng et al., 2011). Together, these data suggest that functional alterations in the DMN and salience network may contribute to an endophenotype that is common to both autism and depression and warrant future cross-diagnostic research.

Included in understanding how depression develops in autism is the question of how to identify individuals who are at risk. The design of the current study does not allow for assessment of directionality to understand if intense circumscribed interests make one prone to developing depression or whether these patterns of repetitive behavior develop in tandem. However, in this sample, individuals with high intensity circumscribed interests also displayed patterns of attention that have previously been shown to map onto depression diagnosis and severity of depression (Duque, 2015). Therefore, this paradigm may prove useful as an assessment of risk for development of depression in future studies that incorporate longitudinal designs.

This paradigm may also be particularly useful for measuring depression in individuals who are unable to access traditional methods of diagnosis, including self-report measures, and therefore excluded from our current understanding of depression in ASD (Gotham et al., 2015). The current study included only individuals at or above a 5th grade reading level, who demonstrated average levels of intelligence. Such were necessary requirements for validation of the task in its relationship to depressive symptomology in our ASD sample. Future studies are necessary to determine the generalizability of this task across levels of adaptive functioning.

Patterns of repetition play a critical role in both the onset and maintenance of depression and in the expression of autism. The increased incidence of depression in autism suggests that while these symptoms differ superficially, they may share common neural mechanisms. In the current study, I used an emotional bias task to reveal similarities between autism and depression in visual attention. I further demonstrated increased rates of depression-related repetitive behavior

in individuals who showed similarly high patterns of autism-specific repetitive behavior. These commonalities suggest susceptibilities in ASD that may be co-opted to result in the onset of depression.

REFERENCES

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, *31*(1), 5–17.

Beck, A. T., Steer, R. A., Brown, G. K., & others. (1996). Beck depression inventory. Retrieved from http://www.nctsnet.org/content/beck-depression-inventory-second-edition

Berman, M. G., Misic, B., Buschkuehl, M., Kross, E., Deldin, P. J., Peltier, S., … others. (2014). Does resting-state connectivity reflect depressive rumination? A tale of two analyses. *Neuroimage*, *103*, 267–279.

Buck, T. R., Viskochil, J., Farley, M., Coon, H., McMahon, W. M., Morgan, J., & Bilder, D. A. (2014). Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(12), 3063–3071.

Burrows, C. A., Usher, L. V., Schwartz, C. B., Mundy, P. C., & Henderson, H. A. (2016). Supporting the Spectrum Hypothesis: Self-Reported Temperament in Children and Adolescents with High Functioning Autism. *Journal of Autism and Developmental Disorders*, *46*(4), 1184–1195.

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., … others. (2013). Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biological Psychiatry*, *74*(12), 898–907.

Constantino, J. N., & Gruber, C. P. (2002). The social responsiveness scale. *Los Angeles: Western Psychological Services*.

Donaldson, C., Lam, D., & Mathews, A. (2007). Rumination and attention in major depression. *Behaviour Research and Therapy*, *45*(11), 2664–2678.

Dozois, D. J., Dobson, K. S., & Ahnberg, J. L. (1998). A psychometric evaluation of the Beck Depression Inventory–II. *Psychological Assessment*, *10*(2), 83.

Duque, A., & Vázquez, C. (2015). Double attention bias for positive and negative emotional faces in clinical depression: Evidence from an eye-tracking study. *Journal of Behavior Therapy and Experimental Psychiatry*, *46*, 107–114.

First, M. B., Gibbon, M., Spitzer, R. L., Benjamin, L. S., & Williams, J. B. (1997). *Structured clinical interview for DSM-IV axis II personality disorders: SCID-II*. American Psychiatric Pub.

Gotham, K., Bishop, S. L., Brunwasser, S., & Lord, C. (2014). Rumination and perceived impairment associated with depressive symptoms in a verbal adolescent–adult ASD sample. *Autism Research*, *7*(3), 381–391.

Gotham, K., Bishop, S. L., Hus, V., Huerta, M., Lund, S., Buja, A., … Lord, C. (2013). Exploring the relationship between anxiety and insistence on sameness in autism spectrum disorders. *Autism Research*, *6*(1), 33–41.

Gotham, K., Unruh, K., & Lord, C. (2015). Depression and its measurement in verbal adolescents and adults with autism spectrum disorder. *Autism*, *19*(4), 491–504.

Gotlib, I. H., & Cane, D. B. (1987). Construct accessibility and clinical depression: A longitudinal investigation. *Journal of Abnormal Psychology*, *96*(3), 199–204.

Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S. L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of Abnormal Psychology*, *113*(3), 386.

Hahamy, A., Behrmann, M., & Malach, R. (2015). The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nature Neuroscience*, *18*(2), 302–309.

Joormann, J., Dkane, M., & Gotlib, I. H. (2006). Adaptive and maladaptive components of rumination? Diagnostic specificity and relation to depressive biases. *Behavior Therapy*, *37*(3), 269–280.

Kaiser, R. H., Whitfield-Gabrieli, S., Dillon, D. G., Goer, F., Beltzer, M., Minkel, J., … Pizzagalli, D. A. (2015). Dynamic resting-state functional connectivity in major depression. *Neuropsychopharmacology*. Retrieved from http://www.nature.com.proxy.library.vanderbilt.edu/npp/journal/vaop/ncurrent/full/npp2015352a.html

Kennedy, D. P., & Courchesne, E. (2008). Functional abnormalities of the default network during self-and other-reflection in autism. *Social Cognitive and Affective Neuroscience*, *3*(2), 177–190.

Kerns, C. M., Roux, A. M., Connell, J. E., & Shattuck, P. T. (2016). Adapting Cognitive Behavioral Techniques to Address Anxiety and Depression in Cognitively Able Emerging Adults on the Autism Spectrum. *Cognitive and Behavioral Practice*, *23*(3), 329–340.

Ko, S.-G., Lee, T.-H., Yoon, H.-Y., Kwon, J.-H., & Mather, M. (2011). How does context affect assessments of facial emotion? The role of culture and age. *Psychology and Aging*, *26*(1), 48.

Lam, K. S., & Aman, M. G. (2007). The Repetitive Behavior Scale-Revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(5), 855–866.

Lam, K. S., Bodfish, J. W., & Piven, J. (2008). Evidence for three subtypes of repetitive behavior in autism that differ in familiality and association with other symptoms. *Journal of Child Psychology and Psychiatry*, *49*(11), 1193–1200.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H., … Dunbar, G. C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224–231.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism diagnostic observation schedule: ADOS-2*. Western Psychological Services Los Angeles, CA.

Lundqvist, D., Flykt, A., & Öhman, A. (1998). The Karolinska directed emotional faces (KDEF). *CD ROM from Department of Clinical Neuroscience, Psychology Section, Karolinska Institutet*, 91–630.

Mattila, M.-L., Hurtig, T., Haapsamo, H., Jussila, K., Kuusikko-Gauffin, S., Kielinen, M., … others. (2010). Comorbid psychiatric disorders associated with Asperger syndrome/high-functioning autism: A community-and clinic-based study. *Journal of Autism and Developmental Disorders*, *40*(9), 1080–1093.

Mazefsky, C. A., Oswald, D. P., Day, T. N., Eack, S. M., Minshew, N. J., & Lainhart, J. E. (2012). ASD, a psychiatric disorder, or both? Psychiatric diagnoses in adolescents with high-functioning ASD. *Journal of Clinical Child & Adolescent Psychology*, *41*(4), 516–523.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology*, *109*(3), 504.

Nolen-Hoeksema, S., & Morrow, J. (1991). A prospective study of depression and posttraumatic stress symptoms after a natural disaster: the 1989 Loma Prieta Earthquake. *Journal of Personality and Social Psychology*, *61*(1), 115.

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on Psychological Science*, *3*(5), 400–424.

Nomi, J. S., & Uddin, L. Q. (2015). Developmental changes in large-scale network connectivity in autism. *NeuroImage: Clinical*, *7*, 732–741.

Schaefer, A., Nils, F., Sanchez, X., & Philippot, P. (2010). Assessing the effectiveness of a large database of emotion-eliciting films: A new tool for emotion researchers. *Cognition and Emotion*, *24*(7), 1153–1172.

Segal, Z. V., Gemar, M., Truchon, C., Guirguis, M., & Horowitz, L. M. (1995). A priming methodology for studying self-representation in major depressive disorder. *Journal of Abnormal Psychology*, *104*(1), 205.

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(8), 921–929.

Treynor, W., Gonzalez, R., & Nolen-Hoeksema, S. (2003). Rumination reconsidered: A psychometric analysis. *Cognitive Therapy and Research*, *27*(3), 247–259.

Turner-Brown, L. M., Lam, K. S. L., Holtzclaw, T. N., Dichter, G. S., & Bodfish, J. W. (2011). Phenomenology and measurement of circumscribed interests in autism spectrum disorders. *Autism*, *15*(4), 437–456. https://doi.org/10.1177/1362361310386507

Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., … Menon, V. (2013). Salience network–based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry*, *70*(8), 869–879.

Van Oppen, P., Hoekstra, R. J., & Emmelkamp, P. M. (1995). The structure of obsessive-compulsive symptoms. *Behaviour Research and Therapy*, *33*(1), 15–23.

Weng, S.-J., Carrasco, M., Swartz, J. R., Wiggins, J. L., Kurapati, N., Liberzon, I., … Monk, C. S. (2011). Neural Activation to Emotional Faces in Adolescents with Autism Spectrum Disorders. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *52*(3), 296. https://doi.org/10.1111/j.1469-7610.2010.02317.x

CHAPTER 7

ENHANCED NEURAL RESPONSE TO NONSOCIAL INFORMATION, BUT NOT SOCIAL, DIFFERENTIATES ADULTS WITH AUTISM FROM NEUROTYPICAL CONTROLS

Introduction

Autism spectrum disorder (ASD) is diagnosed based on deficient social-communicative behavior as well as the presence of restricted and repetitive behaviors and interests. Converging evidence from behavioral, electrophysiological, and functional imaging research indicates that reward is altered in individuals with ASD. Altered function of reward circuitry plays a critical role in the pathophysiology of a variety of neuropsychiatric and neurological disorders, including obsessive compulsive disorder, Parkinson's disease, schizophrenia, and addiction (Cilia et al., 2010; Graybiel & Rauch, 2000; Noble, 2000; Whitton, Treadway, & Pizzagalli, 2015). The wide range of symptom profiles across these diagnoses highlights the malleability of reward processes and their pervasive role in shaping behavior. Similarly, understanding altered processing of reward as an endophenotype in ASD may begin to elucidate the diverse symptom profile seen within this one diagnosis.

Although clear evidence exists to suggests that reward is divergent in autism, compared to typical development (TD), these differences may be highly dependent upon both reward content and reward component. Reward has most thoroughly been studied in ASD for response to social information. The social motivation theory of autism hypothesizes that motivation to pursue and

engage with social information very early in life contributes to a dearth in social experiences, and therefore a lack of the critical opportunities necessary to develop socio-communicative skills. Indeed, children with ASD show deficient social orienting (Dawson et al., 2004) and response to joint attention (e.g., Mundy, Sigman, & Kasari, 1994). Further, studies of functional reward circuitry have found that, in some contexts, neural responsivity to social information differs in ASD, compared to TD peers (Delmonte et al., 2012; Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Goldberg et al., 2016; Kohls, Schulte-Rüther, et al., 2012). In addition to these known deficits, there are clear examples of intact reward in individuals with ASD. Notably, modulation of neural responses to primary reward (food) does not appear to differ between individuals with ASD and TD peers (Cascio et al., 2012). Similarly, it is well-documented that individuals with ASD show increased task performance following the availability or presentation of certain incentives (e.g., Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2011; Lin, Rangel, & Adolphs, 2012; Pankert, Pankert, Herpertz-Dahlmann, Konrad, & Kohls, 2014) and will exert increased effort to obtain certain types of reward (Damiano, Aloi, Treadway, Bodfish, & Dichter, 2012; Ewing, Pellicano, & Rhodes, 2013; Watson et al., 2015).

There is a growing body of literature to suggest that reward in ASD may be *enhanced* to specific types of information. Couple with decreased social behavior, individuals with ASD show *increased* patterns of restricted and repetitive behavior. Specifically, many individuals exhibit circumscribed interests, which unlike other types of repetitive behavior, may be pathognomonic to ASD. Circumscribed interests (CI) have been shown to be primarily nonsocial in nature, are often engaged with in solitude, and are associated with increased functional impairment, compared to interest of TD peers (Baron-Cohen & Wheelwright, 1999; South, Ozonoff, &

McMahon, 2005; Turner-Brown, Lam, Holtzclaw, Dichter, & Bodfish, 2011). Individuals with ASD show increased visual preference for CI-related information (Elison, Sasson, Turner-Brown, Dichter, & Bodfish, 2012; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011; Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008; Sasson & Touchstone, 2014; Unruh et al., 2016) as well as increased responsivity of reward circuitry (Cascio et al., 2014; Foss-Feig et al., 2016), even when stimuli are not specific to the individual's own CI (Dichter, et al., 2012). Critically, there is evidence to suggest that the presence of certain types of CI-related information may actually interfere with attention to and engagement with social information (Elison et al., 2012; Sasson et al., 2011, 2008; Sasson & Touchstone, 2014; Unruh et al., 2016).

It is well established in literature outside of ASD that reward is not unitary (Berridge & Robinson, 1998). Rather, reward can be dissociated into anticipatory and consummatory processes, each of which is facilitated by distinct neurochemicals and neural regions (Berridge, Venier, & Robinson, 1989; Knutson, Fong, Adams, Varner, & Hommer, 2001; Smith, Berridge, & Aldridge, 2011; Yun, Wakabayashi, Fields, & Nicola, 2004). Therefore, differential disruption of these reward components can lead to a variety of behavioral outcomes. A notable model for this differential disruption is addiction, where enhanced anticipatory reward has been shown to contribute to the perpetuation of addiction pursuit / drug-taking behavior (via drug craving) rather than enhanced consummatory responses to behaviors / substances of addiction (Volkow et al., 1995). Importantly, pursuit of and engagement with these behaviors / items of addiction, has been shown to interfere with engagement in other (often adaptive) types of behavior (Esch & Stefano, 2004; Petry, 2006; Smith & Robbins, 2013; Young, 1998). To date, only two studies in

ASD have attempted to dissociate anticipatory and consummatory responses to CI-related information (Benning et al., 2016; Dichter, et al., 2012).

The late positive potential (LPP) is an event related potential (ERP) that indexes motivational salience. The LPP is modulated by the affective content of a stimulus, showing larger responses to positive and negative information, compared to neutral. Joint ERP-fMRI suggest the neural generators of the LPP are regions relevant primarily for anticipatory aspects of reward, including the left orbitofrontal cortex, bilateral amygdala, and insular cortex. Further, this response may specifically reflect the allocation of motor or cognitive / attentional resources to response to or engage with the content in presentation. In line with this, studies in addiction have shown that disorder-specific items (e.g., cigarettes, cocaine, food) are associated with increased motivational salience, compared to other types of affective information. The purpose of the current study was to measure the LPP in response to CI-related information in individuals with ASD. This response was assessed in the context of both typically motivating (social) and neutral information to determine differences in reward responsivity between ASD and typical development. As such, I hypothesized that adults with TD would show increased LPP responses to social stimuli, compared to neutral and CI-related stimuli. Further, I hypothesized that individuals with ASD would show greater responses to CI-related stimuli than TD adults, indicating enhanced anticipatory reward for nonsocial information that is specific to autism.

Methods

Participants

Two groups of adults participated in this study: 10 with ASD (2 females) and 13 who were typically developing (TD; 2 females). All participants met the following general inclusion criteria: age between 18 and 35 years; intelligence quotient (IQ) greater than 80; absence of seizure disorder, acute medical, or genetic condition, and no history or concerns of psychotic or bipolar disorders, current substance use disorders; and absence of any visual impairment uncorrectable with eyeglasses. Participants in the TD cohort were recruited via mass email to the Vanderbilt and greater middle Tennessee area. Individuals with ASD were recruited via email, recruitment flyer, and through various Vanderbilt clinics and pre-existing research studies. Eligibility for participants in the ASD group included confirmed diagnosis of an autism spectrum disorder. Diagnostic status was confirmed through administration of the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2; Lord et al., 2012). Table 7.1 provides demographic information by cohort.

Table 7.1 *Demographics and Participant Characterization for Study 6*

Characteristic	ASD (N = 10)	TD (N = 13)
Age (years)	22.8 (4.1)	24.8 (8.1)
Gender	8 M / 2 F	11 M / 2 F
Full Scale IQ	102.8 (17.8)	112.7 (15.9)
Autism Diagnostic Observation Schedule		
Social + Communication	6.0 (2.9)	--
Stereotyped Behavior + Restricted Interest	5.4 (2.6)	--
Total Severity	5.8 (3.2)	--

ASD, Autism Spectrum Disorder; *TD*; typically developing; *M*, male; *F*; female

Stimuli and task

The current study employed a passive viewing task, comprised 60 static, high quality color images from three stimulus categories: social (SOC), high autism interest (HAI) and neutral (NEU). Refer to Figure 7.1 for task schematic. Images were modified to be equal in size (approximately 550 x 350 pixels) and were always displayed in the center of the screen. Stimulus images were intentionally reduced in size from the full dimension of the screen (1920 x 1080) to limit opportunities for eye movement artifacts. Social images were taken with permission from the MacArthur Foundation Research Network on Early Experience and Brain Development (Tottenham et al., 2009). Identities of the faces did not repeat, were split evenly between males and females, and consisted of Caucasian, African-American, and Asian-American. HAI stimuli were selected to represent items frequently occurring as topics of CI in ASD (South et al., 2005). In previous work in our lab has validated the reward value of these stimuli using standardized valence and arousal ratings. These stimuli were rated by participants with ASD as significantly higher in valence than control object images (Sasson, Dichter, & Bodfish, 2012). Examples of HAI objects include: trains, vehicles, airplanes, clocks, and electronic equipment. Neutral stimuli were comprised of simple furniture, including images of chairs and chests of drawers. Furniture was chosen as a neutral image category based on the previously described independent study of arousal and valence between ASD and TD (Sasson et al., 2012). Two categories of furniture were included to better approximate the image heterogeneity within the HAI category such that one category of stimuli was not more predictable than the others.

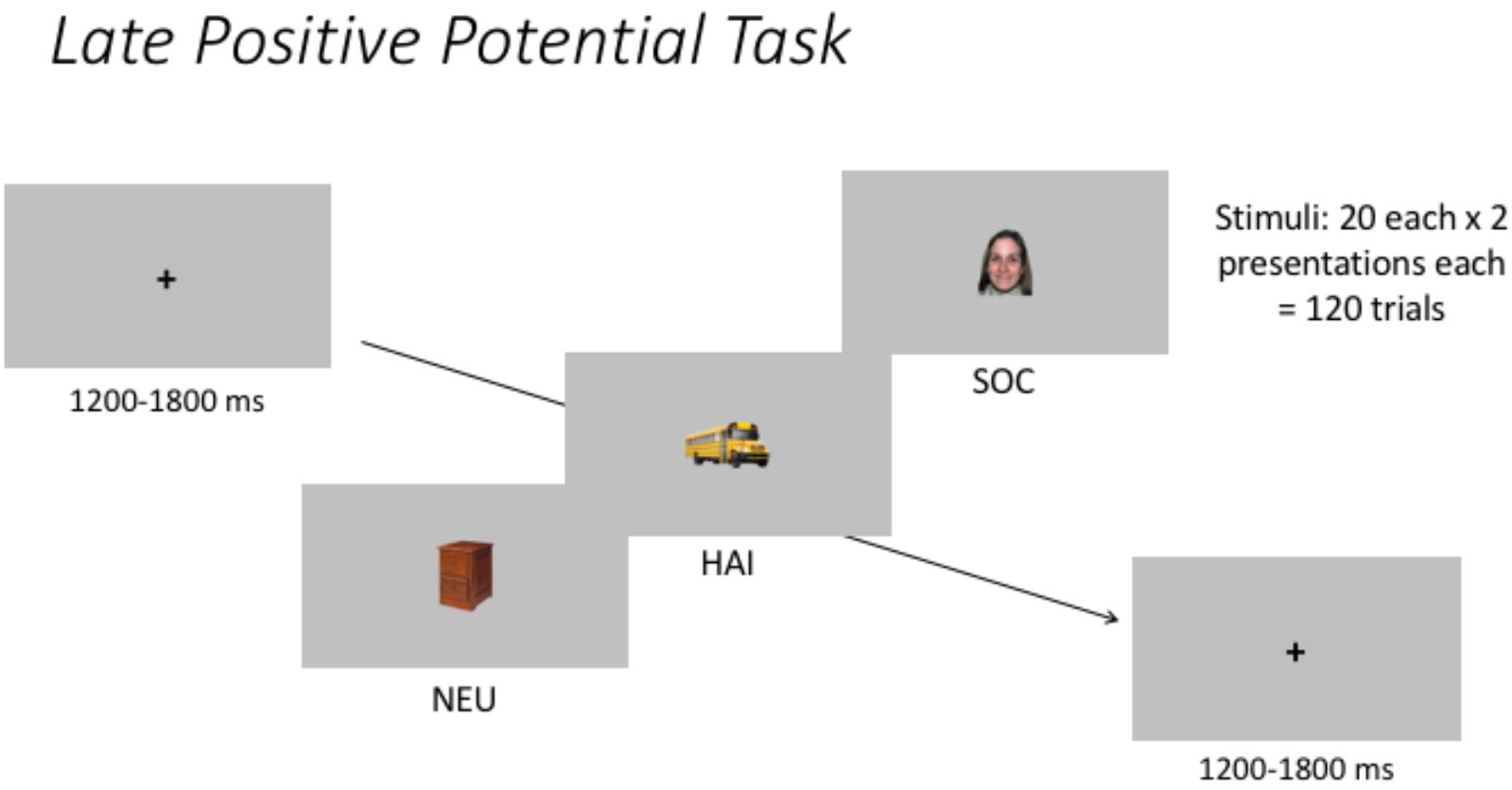

Figure 7.1 **Schematic of the late positive potential task.** *SOC,* social; *HAI*, high autism interest; *NEU*, neutral

Each trial consisted of a variable 1200-1800 ms interstimulus period, during which a fixation cross was presented in the center of the screen, followed by a 2000 ms presentation of an image from the stimulus set. Images were presented twice semi-randomly (no single image was presented consecutively) throughout the duration of the task, comprising 120 total trials. Participants were seated an average of 3-4 feet from the monitor, with the goal of placement at an optimal distance to foveate each stimulus image in its entirety and therefore reducing eye-movement artifacts. Participants were told they would be viewing a series of objects and faces and that they should view the stimuli naturally. Participants were instructed remain as still, but as relaxed as possible, as to minimize artifacts from movement and / or muscle activity. Data was monitored online during recording to ensure high quality recording. If the experimenter noticed obvious deviations from study protocol (e.g., tapping fingers, clenching the jaw, raising eyebrows), the task was paused and the participant was given instructions for behavior modification. As the LPP does not habituate (Schupp, Flaisch, Stockburger, & Junghöfer, 2006), the task was re-administered for participants who did not appear to meet the minimum number of artifact-free trials.

Data collection and analysis

Continuous EEG was recorded from the scalp at 250 Hz, using a high-density array of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net, EGI, Inc., Eugene, OR). Recording began following adjustment of electrode impedances to below 50 kΩ. During online recording, data was referenced to the vertex with filters set at .1-100 Hz.

Offline analysis of ERPs was conducted using Net Station 5.3 Software. All data were band-pass filtered with cut-offs at .1 and 30 Hz. Continuous EEG data was segmented to 200 ms prior to stimulus onset and 2000 ms post-stimulus onset. Single trial epochs were corrected for artifacts, including blinks and eye-movements, using Net Station 5.3 software, as well as through manual inspection. Artifacts were further defined as any channel for which voltage exceeded 200 μV, eye-channel voltages exceeding 140 μV (eye blink), and a pattern of strong opposing polarities between eye-channels (eye-movements). Trial rejection was determined by the presence of an eye blink or eye movement, or any trial for which "bad channels" exceeded 10%. For all included trials, Net Station 5.3 was used to apply an algorithm to correct for bad channels. Data was further baseline corrected using a 200 ms baseline and re-referenced to linked mastoids. ERPs were constructed by separately averaging artifact-free data between stimulus categories (social, HAI, neutral). ERP data was included for a participant if he or she maintained at least 8 trials per stimulus category (Moran, Jendrusina, & Moser, 2013).

The LPP is shown to be maximal at centro-parietal recording sites. However, previous studies using disorder-specific stimuli have shown that responses to such images may be more maximal at fronto-central recording sites (Dunning et al., 2011; Franken et al., 2008; Littel & Franken, 2007). For this reason, LPP responses were compared both between category at each of these recording sites, as well as within category and between participants to assess potential diagnostic and category-specific differences in topography of the signal. The frontal LPP was scored as average activity at electrodes surrounding Fz, including those that correspond to international 10-10 electrode positions Fz, F1, and F2 (Luu & Ferree, 2005). Likewise, the central LPP was scored as average activity at electrodes surrounding Cz, also including CP1 and CP2. The

parietal LPP was scored as the average activity at Pz, P1, P2, POz, PO3, and PO4. Electrode selection for frontal and parietal electrodes were confirmed using both global visual analysis of a topographic plot of all waveforms, as well as spatial principal components analysis (PCA). PCA was conduced across all participants, time points, and conditions. Application of the scree plot suggested that a 3-factor solution was most appropriate for the data set. Based upon these components, Varimax was used to rotate the simple structure. Electrodes included in the analyses displayed loadings of at least .8 onto each respective factors. Central electrode selection was based on global visual analysis of the topographic waveform and *a priori* hypotheses based on a previous study of the LPP in ASD (Benning et al., 2016).

Previous studies have used multiple time windows to assess the magnitude of the LPP response. The LPP is generally considered to be a sustained positivity that begins around 400-600 ms post-stimulus onset (Schupp et al., 2006), often persisting throughout the duration of the stimulus presentation. Often this response is divided into early and late components, although the definition of these time windows is inconsistent across studies. Further, factor analysis suggests that the LPP may in fact be largely consistent with the P300 response until around 600 ms (Foti, Hajcak, & Dien, 2009). For these reasons, a temporal PCA was performed, using methods similar to the previously described spatial PCA. This analysis was conducted across all participants and all time points, but collapsed into the aforementioned electrode factors. Based on this analysis, the LPP was scored for both early (600-800 ms), middle (800-1100 ms) and late (1100-1900 ms) time segments.

Data from all stimuli were included in analyses. LPP mean amplitudes at each time window and electrode were analyzed using a 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) repeated-measures analysis of variance (RM-ANOVA). Initial omnibus analyses were performed to determine the presence of an LPP response, which was indicated by a significant difference between affective (SOC or HAI) and neutral stimuli. Post-hoc pairwise comparisons for condition were adjusted using Tukey's Least Significant Difference. Primary analyses were followed up a series of one-way ANOVAs to address *a priori* hypotheses of differing LPP amplitudes to SOC or HAI stimuli between groups.

Results

Averaged EEG recordings for all electrode location of interest (Fz, Cz, Pz) are presented in Figure 7.2.

Frontal (Fz) LPP

Early time window (600-800 ms)

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = 1.504$, $p = .236$). Mean differences are presented in Figure 7.3a. There was no main effect of condition ($F(1, 36) = 1.412$, $p = .257$). There was a marginally significant main effect of group ($F(1, 18) = 2.09$, $p = .058$, partial $\eta^2 = .185$). Follow-up univariate ANOVA revealed that this effect was qualified by participants with ASD showing a significantly greater amplitude for HAI ($F(1, 18) = 4.429$, $p = .05$, partial $\eta^2 = .197$), but not SOC ($F(1, 18) = 2.695$, $p = .118$) or NEU ($F(1, 18) = 1.137$, $p = .256$), compared to TD participants.

Middle time window (*800-1100 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed a significant condition x group interaction ($F(2, 36) = 3.394$, $p = .045$, partial $\eta^2 = .159$). Mean differences are presented in Figure 7.3b. There was also a main effect of condition ($F(1, 36) = 3.894$, $p = .027$, partial $\eta^2 = .178$), but no main effect of group ($F(1, 18) = 2.878$, $p = .107$). Post-hoc pairwise comparisons indicated that both SOC ($p = .005$) and HAI ($p = .048$) amplitudes were greater than NEU. However, follow-up univariate ANOVA revealed that this effect was qualified by participants with ASD demonstrated a significantly greater amplitude for SOC ($F(1, 18) = 4.838$, $p = .041$, partial $\eta^2 = .212$) and marginally greater effect for HAI ($F(1, 18) = 3.132$, $p = .094$, partial $\eta^2 = .148$), but not NEU ($F(1, 18) = .035$, $p = .848$), compared to TD participants.

Late time window (*1100-1900 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = 1.879$, $p = .165$). Mean differences are presented in Figure 7.3c. There was a main effect of condition ($F(1, 36) = 3.337$, $p = .047$, partial $\eta^2 = .157$), but no main effect of group ($F(1, 18) = 2.521$, $p = .130$). Post-hoc pairwise comparisons indicated that both SOC ($p = .028$) and HAI (marginal significance; $p = .058$) amplitudes were greater than NEU. Follow-up univariate ANOVA further revealed that participants with ASD demonstrated a marginally greater amplitude for HAI ($F(1, 18) = 3.373$, $p = .083$, partial $\eta^2 = .158$), but not SOC ($F(1, 18) = 2.240$, $p = .152$) or NEU ($F(1, 18) = .008$, $p = .928$), compared to TD participants.

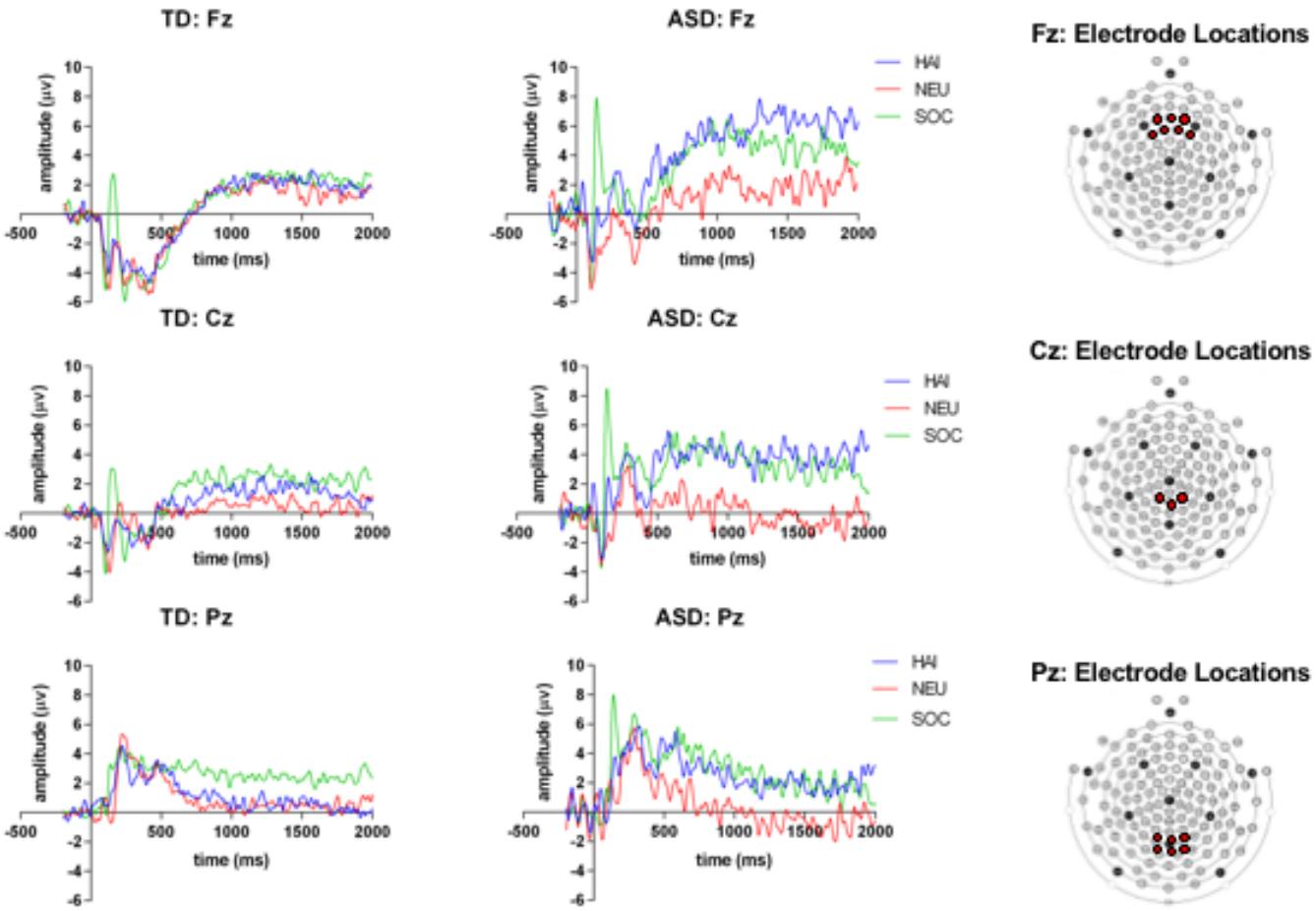

Figure 7.2 **Averaged EEG recordings for frontal, central, and parietal electrode locations.** *ASD,* Autism Spectrum Disorder; *TD*, typical development; *Fz,* frontal electrode locations; *Cz*, central electrode locations; *Pz*, parietal electrode locations.

Central (Cz) LPP

Early time window (*600-800 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = 1.159$, $p = .325$). Mean differences are presented in Figure 7.4a. There was a main effect of condition ($F(1, 36) = 5.827$, $p = .006$, partial $\eta^2 = .245$), but no main effect of group ($F(1, 18) = 2.736$, $p = .115$). Post-hoc pairwise comparisons indicated that both SOC ($p = .010$) and HAI ($p = .007$) amplitudes were greater than NEU. Follow-up univariate ANOVA further revealed that participants with ASD demonstrated a greater amplitude for HAI ($F(1, 18) = 5.921$, $p = .026$, partial $\eta^2 = .248$), but not SOC ($F(1, 18) = 1.386$, $p = .254$) or NEU ($F(1, 18) = .306$, $p = .587$), compared to TD participants.

Middle time window (*800-1100 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = 1.366$, $p = .268$). Mean differences are presented in Figure 7.4b. There was a main effect of condition ($F(1, 36) = 6.614$, $p = .004$, partial $\eta^2 = .269$), but no main effect of group ($F(1, 18) = 1.789$, $p = .198$). Post-hoc pairwise comparisons indicated that both SOC ($p = .008$) and HAI ($p = .009$) amplitudes were greater than NEU. Follow-up univariate ANOVA further revealed that participants with ASD demonstrated a marginally greater amplitude for HAI ($F(1, 18) = 3.882$, $p = .064$, partial $\eta^2 = .177$), but not SOC ($F(1, 18) = 1.479$, $p = .240$) or NEU ($F(1, 18) = .003$ $p = .959$), compared to TD participants.

Late time window (*1100-1900 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = 1.929$, $p = .160$). Mean differences are presented in Figure 7.4c. There was a main effect of condition ($F(1, 36) = 7.085$, $p = .003$, partial $\eta^2 = .282$), but no main effect of group ($F(1, 18) = .360$, $p = .556$). Post-hoc pairwise comparisons indicated that both SOC ($p = .004$) and HAI ($p = .011$) amplitudes were greater than NEU. Follow-up univariate ANOVA further revealed no group differences for any stimulus condition (all ps > .15).

Parietal (Pz) LPP

Early time window (*600-800 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = .752$, $p = .347$). Mean differences are presented in Figure 7.5a. There was a main effect of condition ($F(1, 36) = 7.113$, $p = .002$, partial $\eta^2 = .283$), but no main effect of group ($F(1, 18) = .743$, $p = .400$). Post-hoc pairwise comparisons indicated that both SOC ($p = .002$) and HAI ($p = .043$) amplitudes were greater than NEU. Follow-up univariate ANOVA further revealed no group differences for any stimulus condition (all ps > .15).

Middle time window (*800-1100 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = .633$, $p = .537$). Mean differences are presented in Figure 7.5b. There was a main effect of condition ($F(1, 36) = 5.963$, $p = .006$, partial $\eta^2 = .249$), but no main effect of group ($F(1, 18) = .464$, $p = .504$). Post-hoc pairwise comparisons indicated that both SOC ($p = .008$) and HAI (marginal significance; $p = .052$) amplitudes were greater than NEU.

Follow-up univariate ANOVA further revealed no group differences for any stimulus condition (all *p*s > .19).

Late time window (*1100-1900 ms)*

A 3 (Category: SOC, HAI, NEU) x 2 (Group: TD, ASD) RM-ANOVA revealed no condition x group interaction ($F(2, 36) = 1.261$, $p = .296$). Mean differences are presented in Figure 7.5c. There was a main effect of condition ($F(1, 36) = 3.865$, $p = .030$, partial $\eta^2 = .177$), but no main effect of group ($F(1, 18) = .064$, $p = .909$). Post-hoc pairwise comparisons indicated that SOC ($p = .019$), but not HAI ($p = .163$) amplitudes were greater than NEU. Follow-up univariate ANOVA further revealed no group differences for any stimulus condition (all *p*s > .23).

Within-group comparisons

A set of paired samples t-tests were performed to determine within-group differences in LPP response to SOC and HAI stimuli. Participants with ASD showed no difference between conditions for any location at any time point (all *p*s > .5). Participants with TD showed no differences for frontal or central electrodes (all *p*s > .17). For parietal electrodes, participants with TD showed significantly greater LPP amplitudes to SOC than HAI across all time points (early, $t = 2.463$, $p = .032$; middle, $t = 2.494$, $p = .030$; late, $t = 3.413$, $p = .006$). Mean differences are represented in Figure 7.5.

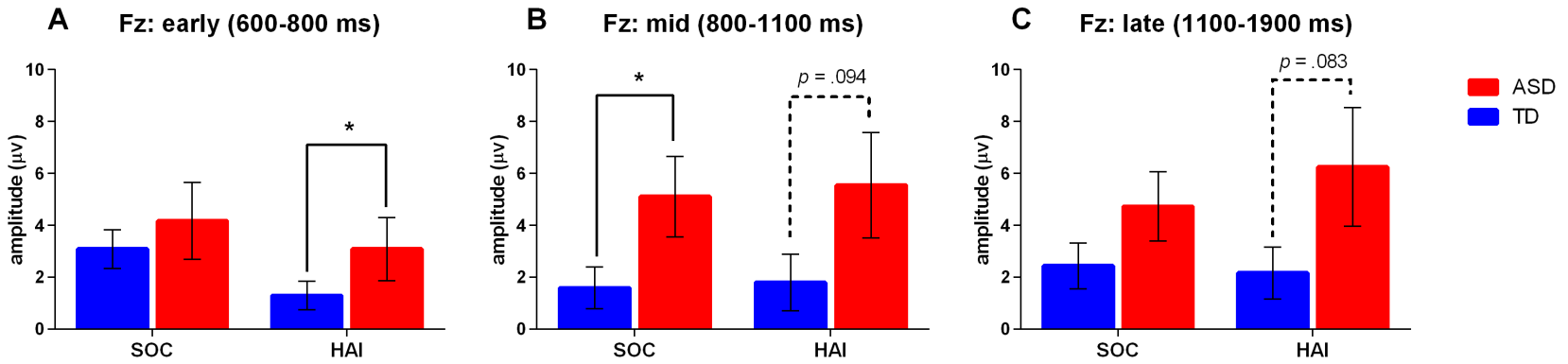

Figure 7.3 **Average LPP amplitudes at frontal electrodes for ASD and TD participants. (A)** Participants with ASD demonstrate greater LPP amplitudes to HAI images at frontal electrodes during the early time window. **(B)** Participants with ASD demonstrate greater LPP amplitudes to SOC and HAI images at frontal electrodes during the middle time window. **(C)** Participants with ASD demonstrate marginally greater LPP amplitudes to HAI images at frontal electrodes during the late time window. Error bars represent standard error of the mean. *, $p < .05$; *ASD,* Autism Spectrum Disorder; *TD*, typical development; *Fz,* frontal electrode locations; *HAI*, high autism interest; *SOC*; social

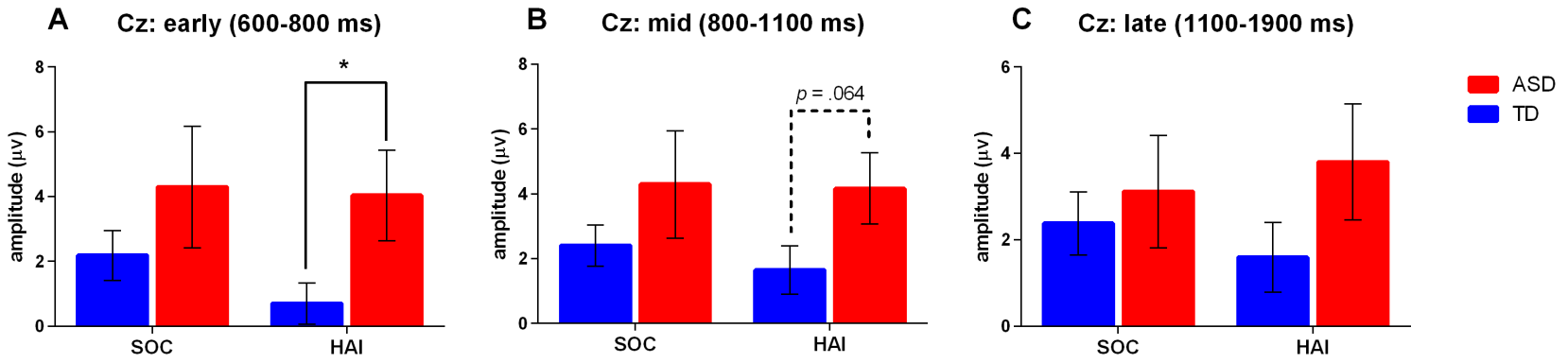

Figure 7.4 **Average LPP amplitudes at central electrodes for ASD and TD participants. (A)** Participants with ASD demonstrate greater LPP amplitudes to HAI images at central electrodes during the early time window. **(B)** Participants with ASD demonstrate greater LPP amplitudes to HAI images at central electrodes during the middle time window. **(C)** LPP amplitudes at central electrodes do not differ across participants during the late time window. Error bars represent standard error of the mean. *, $p < .05$; *ASD,* Autism Spectrum Disorder; *TD*, typical development; *Cz,* central electrode locations; *HAI*, high autism interest; *SOC*; social

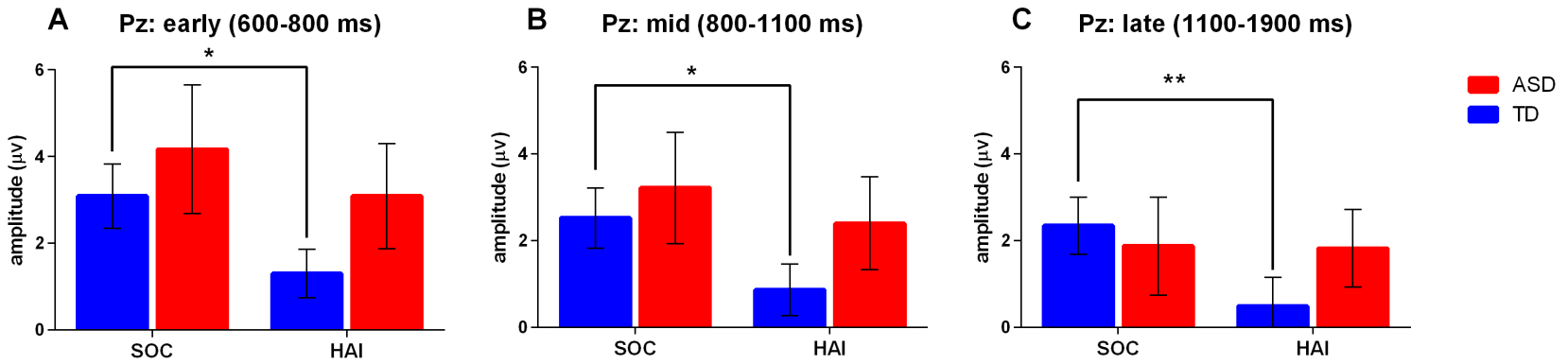

Figure 7.5 **Average LPP amplitudes at parietal electrodes for ASD and TD participants. (A)** Participants with TD demonstrate greater LPP amplitudes to SOC than to HAI images at parietal electrodes during the early time window. **(B)** Participants with TD demonstrate greater LPP amplitudes to SOC than to HAI images at parietal electrodes during the middle time window. **(C** Participants with TD demonstrate greater LPP amplitudes to SOC than to HAI images at parietal electrodes during the late time window. Error bars represent standard error of the mean. *, $p < .05$; **, $p < .01$; *ASD,* Autism Spectrum Disorder; *TD*, typical development; *Pz,* parietal electrode locations; *HAI*, high autism interest; *SOC*; social

Discussion

The presence of circumscribed interests in the ASD phenotype suggests an enhancement of reward to specific types of information that are primarily nonsocial in content. The purpose of this study was to compare neural responses to social and nonsocial stimuli in adults with and without autism using an ERP index of motivational salience, the late positive potential. I hypothesized that adults with ASD would show relatively larger LPP responses to nonsocial stimuli, compared to social or neutral, while adults with TD would show larger responses to social, compared to other stimulus categories. Larger LPP responses to social stimuli, compared to HAI and NEU stimuli were observed for adults with TD. Further, adults with ASD demonstrated larger LPP responses to HAI stimuli, compared to adults with TD.

LPP responses were examined across three electrode locations. Although the LPP is most commonly known to be reflected in centro-parietal regions (Schupp et al., 2006), there is some evidence that LPP modulation to disorder-specific stimuli (compared to standard affective categories) may be reflected more broadly in fronto-central regions (Dunning et al., 2011; Franken et al., 2008; Littel & Franken, 2007). For this reason, frontal, central, and parietal midline electrode clusters were included in analyses, although location-related hypotheses were exploratory. Analysis of Pz electrodes revealed an overall pattern of greater LPP amplitudes to social and HAI stimuli compared to neutral; however, no differentiation was observed between groups for either stimulus condition. In contrast, at Cz electrodes, social responses were not differentiable between groups, while HAI responses were greater in adults with ASD. Finally, omnibus analyses revealed significant effects of social and HAI categories at Fz electrodes only for participants with ASD. This pattern may be suggestive of a broader dispersion of the LPP

signal in adults with ASD, although the implications of such an effect are largely unknown. One hypothesis is that frontally distributed LPP responses are associated with increased reactivity to reward cues, a process mediated by regions of the prefrontal cortex that is involved in the pathogenesis of other reward-related disorders (Wilson, Sayette, & Fiez, 2004).

There is currently one published study that has examined LPP responses in ASD to social and autism-specific (HAI) information. Benning et al (2016) used face and CI-related stimuli to measure LPP responses in young adolescents with ASD across 3 midline electrodes (Fz, Cz, and Pz) and found LPP response specificity at the central location. Adolescents with ASD demonstrated greater HAI responses and smaller social responses than TD peers, although overall social responses were greater to social stimuli than HAI in both groups. Importantly, however, this study did not include a neutral comparison condition, to determine the presence or absence of a differentiated affective response. The current study provides evidence that converges with this previous study, reflecting the presence of a significant LPP to autism-specific information in ASD that is apparent at central, but not parietal electrode locations. However, in the current study, LPP responses to social information did not differ across groups. This may be reflective of developmental differences between the two groups (adolescents versus adults), although this may also be due to differences in power, given the small sample size of the current study.

In this study, adults with ASD demonstrated LPP responses to social stimuli that were significantly greater than responses to neutral and that did not differ in amplitude to LPP responses to social stimuli in TD control participants. The literature regarding reward

responsivity to social information in ASD is mixed, with some studies finding diminished anticipatory and / or consummatory neural responses to social reward (Delmonte et al., 2012; Zeeland et al., 2010) and others finding no differences compared to typical development (Dichter, et al., 2012; Kohls, et al., 2012). Multiple factors likely contribute to these inconsistencies, with two primary considerations being the age of the study sample and the reward component being measured. The data here suggests that verbally fluent adults with ASD may show intact social "wanting," in contrast to existing theories of diminished social motivation in ASD (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson, 1991; Kohls, Chevallier, Troiani, & Schultz, 2012). The current results are also in line with the eye-tracking studies that have examined preference for viewing social and nonsocial stimuli in ASD (Unruh et al 2016; Sasson & Touchstone 2014) and have found that children with ASD view social images in similar manner to their non-ASD peers when social images did not compete for attention with nonsocial images. Together, these results do not support a simple model of social motivation deficits in ASD, but instead suggest that a dynamic relationship exists between social and nonsocial reward-related information in ASD.

Importantly, the current study did not reveal significant differences in LPP amplitude to nonsocial, compared to social stimuli in participants with ASD. There are several potential interpretations for this finding. One is that unlike in typical development, where there is a preferential response to social information, social and nonsocial salience are not different in ASD. This interpretation would suggest that the motivational deficit in ASD involves a failure to clearly distinguish reward-related information such that a preference for social stimulation cannot arise. Alternatively, differential responses to social and nonsocial stimuli may not be

present when these types of stimuli do not compete for attention – as in the single picture viewing method used in the present study. This later interpretation is more in line with results from previous studies that used contextual reward paradigms to force attentional "choices" between stimulus categories (e.g., paired preference measured from a social versus nonsocial array, or foraging / exploration response measured using an array of social and nonsocial stimuli). For example, previous studies of preferential viewing in ASD suggest that attention to and preference for social stimuli is not atypical in ASD in conditions where the social stimuli are not paired with highly preferred nonsocial (Sasson & Touchstone, 2014; Unruh et al., 2016). These demonstrations that processing of social stimuli may be typical in ASD under some conditions, are intriguing because they suggest that the social deficits that are core features of ASD may be more plastic or malleable than often assumed. Continued examination of the possibility that social reward-related processing in ASD is not atypical will be important in light of the common assumption that cognitive and behavioral differences associated with ASD result from a domain-specific deficit in processing social information.

Unlike magnetic resonance imaging (MRI) methods, traditional EEG recording does not allow for precision in source localization to draw conclusions about the neural generators of the response. However, previous studies have utilized multi-method paradigms to understand the neural substrates of the LPP. Such studies have identified the bilateral occipito-temporal junction, insula, amygdala, hippocampus, and temporal poles as regions that are coupled with single trial LPP amplitude (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012). The insula may be of particular relevance for understanding the theoretical significance of the LPP, as well as for interpreting the results of the current study. The insula functions as a primary node of the

salience network, and is involved in attribution of and attention to salient information in the environment (Uddin, 2015; Menon & Uddin, 2010). Importantly, this node / network may work as a modulator between the default mode network and the central executive function network, thereby serving to direct stimulus-driven control of attention (Menon & Uddin, 2010). Therefore, rather than solely reflecting subcortically-generated reward "wanting" responses, which due to their proximal location from the scalp are likely not measured by EEG data collection, the LPP may be better conceptualized as an appetitive response. One demonstrative exemplar of this conceptualization is a study that observed larger LPP responses to food in participants who had fasted, compared to participants who were satiated (Stockburger, Schmälzle, Flaisch, Bublatzky, & Schupp, 2009).

The insula has been implicated in a previous study examining neural reward response to CI-related information in children and adolescents with ASD (Cascio et al., 2014). This region both differentiated patterns of responsivity between participants with ASD and TD peers and was positively correlated with a measure of CI intensity. The current study provides converging evidence of increased responsivity of reward- and salience-related neural mechanisms to autism-specific stimuli. An important difference between Cascio et al (2014) and the current study is the lack of person-specific stimuli. The current study utilized a general category of CI-related stimuli (Sasson et al., 2012). It can be hypothesized that this category likely underestimates neural responsivity to nonsocial reward and such responses would, therefore, be enhanced to individualized stimuli. Another interesting consideration is that the LPP is susceptible to cognitive modulation, such that directing attention to more or less arousing aspects (Hajcak, Dunning, & Foti, 2009) or instructing participants to engage in cognitive reappraisal of stimuli

(Dennis & Hajcak, 2009) can influence the magnitude of the response. It may be informative for future studies to examine how this cognitive modulation of stimulus salience functions in ASD. For example, how is the LPP modulated if individuals are informed that the images they are viewing will later be choices as items with which they may later engage? It may also be relevant to frame social images within a context, by indicating to participants that they will later be partnering with one of these individuals for a cooperative task (see Bublatzky, Gerdes, White, Riemer, & Alpers, 2014).

The current study presents results from a novel passive viewing paradigm for examining neural responses reflective of motivational salience to social and nonsocial stimuli in adults with ASD. In general, neural responses to nonsocial stimuli differentiated groups, with ASD participants showing larger LPP amplitudes to nonsocial images relative to participants with TD. Social images, however, were not differentiable between groups. This pattern of results does not support a domain-specific motivational model of ASD such as the social motivation model; instead, the results are more in line with a dynamic model of motivation in autism where the reward deficit in ASD is best characterized by the nature of the differential response to both social and nonsocial rewards. Further, our results add to previous studies that have examined differential reward-related responses to social and nonsocial information in ASD with results providing converging evidence across several studies for the presence of a measureable reward endophenotype in ASD that may underlie ASD-related differences in cognition and behavior.

REFERENCES

Baron-Cohen, S., & Wheelwright, S. (1999). "Obsessions" in children with autism or Asperger syndrome. Content analysis in terms of core domains of cognition. *The British Journal of Psychiatry*, *175*(5), 484–490. https://doi.org/10.1192/bjp.175.5.484

Benning, S. D., Kovac, M., Campbell, A., Miller, S., Hanna, E. K., Damiano, C. R., … others. (2016). Late Positive Potential ERP Responses to Social and Nonsocial Stimuli in Youth with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *46*(9), 3068–3077.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*(3), 309–369.

Berridge, K. C., Venier, I. L., & Robinson, T. E. (1989). Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function. *Behavioral Neuroscience*, *103*(1), 36.

Bublatzky, F., Gerdes, A., White, A. J., Riemer, M., & Alpers, G. W. (2014). Social and emotional relevance in face processing: happy faces of future interaction partners enhance the late positive potential. *Frontiers in Human Neuroscience*, *8*, 493.

Cascio, C. J., Foss-Feig, J. H., Heacock, J. L., Newsom, C. R., Cowan, R. L., Benningfield, M. M., … Cao, A. (2012). Response of neural reward regions to food cues in autism spectrum disorders. *Journal of Neurodevelopmental Disorders*, *4*(1), 9. https://doi.org/10.1186/1866-1955-4-9

Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P., … Cao, A. (2014). Affective neural response to restricted interests in autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*(2), 162–171.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*(4), 231–239.

Cilia, R., Ko, J. H., Cho, S. S., van Eimeren, T., Marotta, G., Pellecchia, G., … Strafella, A. P. (2010). Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiology of Disease*, *39*(1), 98–104.

Damiano, C. R., Aloi, J., Treadway, M., Bodfish, J. W., & Dichter, G. S. (2012). Adults with autism spectrum disorders exhibit decreased sensitivity to reward parameters when making effort-based decisions. *Journal of Neurodevelopmental Disorders*, *4*, 13. https://doi.org/10.1186/1866-1955-4-13

Dawson, G. (1991). VIII A Psychobiological Perspective on the Early Socio-emotional Development of Children with Autism. *Models and Integrations*, *3*, 207.

Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., & Liaw, J. (2004). Early social attention impairments in autism: social orienting, joint attention, and attention to distress. *Developmental Psychology*, *40*(2), 271.

Delmonte, S., Balsters, J. H., McGrath, J., Fitzgerald, J., Brennan, S., Fagan, A. J., & Gallagher, L. (2012). Social and monetary reward processing in autism spectrum disorders. *Molecular Autism*, *3*(1), 1.

Demurie, E., Roeyers, H., Baeyens, D., & Sonuga-Barke, E. (2011). Common alterations in sensitivity to type but not amount of reward in ADHD and autism spectrum disorders. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *52*(11), 1164–1173. https://doi.org/10.1111/j.1469-7610.2010.02374.x

Dennis, T. A., & Hajcak, G. (2009). The late positive potential: a neurophysiological marker for emotion regulation in children. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *50*(11), 1373–1383. https://doi.org/10.1111/j.1469-7610.2009.02168.x

Dichter, G. S., Felder, J. N., Green, S. R., Rittenberg, A. M., Sasson, N. J., & Bodfish, J. W. (2012). Reward circuitry function in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *7*(2), 160–172.

Dichter, G. S., Richey, J. A., Rittenberg, A. M., Sabatino, A., & Bodfish, J. W. (2012). Reward circuitry function in autism during face anticipation and outcomes. *Journal of Autism and Developmental Disorders*, *42*(2), 147–160.

Dunning, J. P., Parvaz, M. A., Hajcak, G., Maloney, T., Alia-Klein, N., Woicik, P. A., … Goldstein, R. Z. (2011). Motivated attention to cocaine and emotional cues in abstinent and current cocaine users–an ERP study. *European Journal of Neuroscience*, *33*(9), 1716–1723.

Elison, J. T., Sasson, N. J., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2012). Age trends in visual exploration of social and nonsocial information in children with autism. *Research in Autism Spectrum Disorders*, *6*(2), 842–851.

Esch, T., & Stefano, G. B. (2004). The neurobiology of pleasure, reward processes, addiction and their health implications. *Neuroendocrinology Letters*, *25*(4), 235–251.

Ewing, L., Pellicano, E., & Rhodes, G. (2013). Using Effort to Measure Reward Value of Faces in Children with Autism. *PLOS ONE*, *8*(11), e79493. https://doi.org/10.1371/journal.pone.0079493

Foss-Feig, J. H., McGugin, R. W., Gauthier, I., Mash, L. E., Ventola, P., & Cascio, C. J. (2016). A functional neuroimaging study of fusiform response to restricted interests in children and adolescents with autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *8*(1). https://doi.org/10.1186/s11689-016-9149-6

Foti, D., Hajcak, G., & Dien, J. (2009). Differentiating neural responses to emotional pictures: evidence from temporal-spatial PCA. *Psychophysiology*, *46*(3), 521–530.

Franken, I. H., Dietvorst, R. C., Hesselmans, M., Franzek, E. J., Van De Wetering, B. J., & Van Strien, J. W. (2008). CLINICAL STUDY: Cocaine craving is associated with electrophysiological brain responses to cocaine-related stimuli. *Addiction Biology*, *13*(3–4), 386–392.

Goldberg, M. C., Allman, M. J., Hagopian, L. P., Triggs, M. M., Frank-Crawford, M. A., Mostofsky, S. H., … DeLeon, I. G. (2016). Examining the reinforcing value of stimuli

within social and non-social contexts in children with and without high-functioning autism. *Autism*, 1362361316655035. https://doi.org/10.1177/1362361316655035

Graybiel, A. M., & Rauch, S. L. (2000). Toward a neurobiology of obsessive-compulsive disorder. *Neuron*, *28*(2), 343–347.

Hajcak, G., Dunning, J. P., & Foti, D. (2009). Motivated and controlled attention to emotion: time-course of the late positive potential. *Clinical Neurophysiology*, *120*(3), 505–510.

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, *12*(17), 3683–3687.

Kohls, G., Chevallier, C., Troiani, V., & Schultz, R. T. (2012). Social 'wanting'dysfunction in autism: neurobiological underpinnings and treatment implications. *Journal of Neurodevelopmental Disorders*, *4*(10), 1–20.

Kohls, G., Schulte-Rüther, M., Nehrkorn, B., Müller, K., Fink, G. R., Kamp-Becker, I., … Konrad, K. (2012). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, nss033.

Lin, A., Rangel, A., & Adolphs, R. (2012). Impaired Learning of Social Compared to Monetary Rewards in Autism. *Frontiers in Neuroscience*, *6*. https://doi.org/10.3389/fnins.2012.00143

Littel, M., & Franken, I. H. (2007). The effects of prolonged abstinence on the processing of smoking cues: an ERP study among smokers, ex-smokers and never-smokers. *Journal of Psychopharmacology*, *21*(8), 873–882.

Liu, Y., Huang, H., McGinnis-Deweese, M., Keil, A., & Ding, M. (2012). Neural substrate of the late positive potential in emotional processing. *The Journal of Neuroscience*, *32*(42), 14563–14572.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism diagnostic observation schedule: ADOS-2*. Western Psychological Services Los Angeles, CA.

Luu, P., & Ferree, T. (2005). Determination of the HydroCel Geodesic Sensor Nets' Average Electrode Positions and Their 10–10 International Equivalents. *Inc, Technical Note*. Retrieved from ftp://ftp.egi.com/pub/.../pub/documentation/technotes/HydroCelGSN_10-20.pdf

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Moran, T. P., Jendrusina, A. A., & Moser, J. S. (2013). The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Research*, *1516*, 66–75.

Mundy, P., Sigman, M., & Kasari, C. (1994). Joint attention, developmental level, and symptom presentation in autism. *Development and Psychopathology*, *6*(03), 389–401.

Noble, E. P. (2000). Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: a review. *European Psychiatry*, *15*(2), 79–89. https://doi.org/10.1016/S0924-9338(00)00208-X

Pankert, A., Pankert, K., Herpertz-Dahlmann, B., Konrad, K., & Kohls, G. (2014). Responsivity to familiar versus unfamiliar social reward in children with autism. *Journal of Neural Transmission*, *121*(9), 1199–1210. https://doi.org/10.1007/s00702-014-1210-6

Petry, N. M. (2006). Should the scope of addictive behaviors be broadened to include pathological gambling? *Addiction*, *101*(s1), 152–160.

Sasson, N. J., Dichter, G. S., & Bodfish, J. W. (2012). Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PloS One*, *7*(8), e42457.

Sasson, N. J., Elison, J. T., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2011). Brief report: Circumscribed attention in young children with autism. *Journal of Autism and Developmental Disorders*, *41*(2), 242–247.

Sasson, N. J., & Touchstone, E. W. (2014). Visual attention to competing social and object images by preschool children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 584–592.

Sasson, N. J., Turner-Brown, L. M., Holtzclaw, T. N., Lam, K. S., & Bodfish, J. W. (2008). Children with autism demonstrate circumscribed attention during passive viewing of complex social and nonsocial picture arrays. *Autism Research*, *1*(1), 31–42.

Schupp, H. T., Flaisch, T., Stockburger, J., & Junghöfer, M. (2006). Emotion and attention: event-related brain potential studies. *Progress in Brain Research*, *156*, 31–51.

Smith, D. G., & Robbins, T. W. (2013). The Neurobiological Underpinnings of Obesity and Binge Eating: A Rationale for Adopting the Food Addiction Model. *Biological Psychiatry*, *73*(9), 804–810. https://doi.org/10.1016/j.biopsych.2012.08.026

Smith, K. S., Berridge, K. C., & Aldridge, J. W. (2011). Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. *Proceedings of the National Academy of Sciences*, *108*(27), E255–E264.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive Behavior Profiles in Asperger Syndrome and High-Functioning Autism. *Journal of Autism & Developmental Disorders*, *35*(2), 145–158.

Stockburger, J., Schmälzle, R., Flaisch, T., Bublatzky, F., & Schupp, H. T. (2009). The impact of hunger on food cue processing: an event-related brain potential study. *Neuroimage*, *47*(4), 1819–1829.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research*, *168*(3), 242–249.

Turner-Brown, L. M., Lam, K. S. L., Holtzclaw, T. N., Dichter, G. S., & Bodfish, J. W. (2011). Phenomenology and measurement of circumscribed interests in autism spectrum disorders. *Autism*, *15*(4), 437–456. https://doi.org/10.1177/1362361310386507

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, *16*(1), 55–61.

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W. (2016). Social Orienting and Attention Is Influenced by the Presence of Competing Nonsocial Information in Adolescents with Autism. *Frontiers in Neuroscience*, *10*.

Volkow, N. D., Ding, Y.-S., Fowler, J. S., Wang, G.-J., Logan, J., Gatley, J. S., … others. (1995). Is methylphenidate like cocaine?: Studies on their pharmacokinetics and distribution in the human brain. *Archives of General Psychiatry*, *52*(6), 456–463.

Watson, K. K., Miller, S., Hannah, E., Kovac, M., Damiano, C. R., Sabatino-DiCrisco, A., … Dichter, G. S. (2015). Increased reward value of non-social stimuli in children and adolescents with autism. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01026

Whitton, A. E., Treadway, M. T., & Pizzagalli, D. A. (2015). Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry*, *28*(1), 7.

Wilson, S. J., Sayette, M. A., & Fiez, J. A. (2004). Prefrontal responses to drug cues: a neurocognitive analysis. *Nature Neuroscience*, *7*(3), 211–214. https://doi.org/10.1038/nn1200

Young, K. S. (1998). Internet addiction: The emergence of a new clinical disorder. *CyberPsychology & Behavior*, *1*(3), 237–244.

Yun, I. A., Wakabayashi, K. T., Fields, H. L., & Nicola, S. M. (2004). The Ventral Tegmental Area Is Required for the Behavioral and Nucleus Accumbens Neuronal Firing Responses to Incentive Cues. *The Journal of Neuroscience*, *24*(12), 2923–2933. https://doi.org/10.1523/JNEUROSCI.5282-03.2004

Zeeland, S.-V., Ashley, A., Dapretto, M., Ghahremani, D. G., Poldrack, R. A., & Bookheimer, S. Y. (2010). Reward processing in autism. *Autism Research*, *3*(2), 53–67.

CHAPTER 8

GENERAL DISCUSSION

Altered reward in ASD: Toward a dynamic motivation model that incorporates both social and nonsocial reward

Socio-communicative deficits and restricted, repetitive behaviors and interests represent equal domains of the autism phenotype; yet, both research and leading intervention strategies have, to date, primarily focused on addressing the former. This hierarchy has likely been influenced by leading theories of autism that treat these phenotypic characteristics as independent entities. Whether these two diagnostic features possess mechanistic commonalities and how the presence of one influences the developmental trajectory of the other, is largely unknown.

The co-occurrence of both social and nonsocial (restricted, repetitive behaviors and interests) behavioral domains within an individual with ASD demonstrates that they do not occur in isolation. Rather, these domains interact to shape an individual's experiences throughout development. For example, a child's hand-flapping may keep him from engaging in a cooperative play experience with a parent or peer. An adult's propensity to perseverate on discussing his interest in World War II may keep him from developing or maintaining meaningful social relationships. Alternatively, although perhaps less commonly considered, it is possible that parental engagement may function to shape stereotyped or compulsive patterns into more flexible, adaptive behaviors. Similarly, engaging in social relationships may model for an adult with ASD how to expand his or her scope of interest to connect reciprocally with others.

Therefore, even if social and nonsocial behaviors in ASD do not emerge from a shared neural mechanism, engagement in one behavior likely influences the manifestation and development of the other.

The autism phenotype is characterized by both a *deficit* in socio-communicative behavior and an *excess* of restricted, repetitive behavior and interests. Such a pattern of deficiency and excess suggests that avoidance and approach processes may be operative, and therefore points to reward circuitry as a potential contributing and common mechanism in the development and manifestation of the social and nonsocial behaviors that characterize the autism phenotype. Robust evidence from genetics, neurochemistry, and neural connectivity and function implicate reward circuitry in the pathogenesis of autism. However, the functional consequences of reward alterations in autism are less well understood. Here, I have presented and tested a novel framework for considering how underlying alterations in reward circuitry may be co-opted to produce the unique phenotype that is characteristic of ASD.

The dynamic motivation model of autism is based upon the supposition that, in the case of ASD, excessive engagement in nonsocial experiences (e.g., repetitive behaviors and interests that are characteristic of ASD) may "crowd out" opportunities for more social experiences. This altered pattern of experience may, therefore, "canalize" or restrict experience-dependent brain development to favor the development of nonsocial patterns of behavior or skills at the expense of social patterns of behavior or skills. Importantly, the dynamic motivation model moves beyond a simple model for motivational deficits in ASD, and implicates a critical interaction between social and nonsocial approach and engagement. The studies presented here demonstrate

novel methods for testing this model and provide empirical support for conceptualizing the separate social and nonsocial aspects of the autism phenotype as reward-related behaviors.

Summary of findings

The studies presented here provide evidence for altered patterns of reward processing in autism that extend across development and across the range of cognitive function seen in ASD. I utilized a preferential viewing paradigm to measure visual attention to social vs. nonsocial image pairs, thereby creating a "forced choice" (Chapters 2, 4, and 5). Nonsocial images were modulated between arrays, with some representing highly affectively salient objects while others represented objects of neutral valence. This task consistently showed autism-specific effects, such that for several parameters of visual attention that serve as proxies for preference, attention was increased to nonsocial information and decreased to social information, compared to peers of a similar developmental level. A novel finding from these studies was the presence of context-dependent social attention. I observed that adolescents with ASD showed delayed orienting responses to social information, compared to TD peers, only in the context of highly salient objects. Importantly, group differences in visual attention could not be attributed to the influence of low-level salience, suggesting that the preferential viewing task captures top-down driven attentional difference (Chapter 3). I additionally demonstrated enhanced nonsocial reward in ASD via a neural marker of motivational salience (Chapter 7). Adults with ASD demonstrated enhanced late positive potential (LPP) amplitudes to highly salient nonsocial objects, compared to TD adults. Further, adults with ASD showed intact neural responses to social stimuli, compared to TD peers, contrary to previous findings of deficient or diminished social reward in ASD. Finally, I utilized a cross-diagnostic comparison group design to demonstrate that altered

reward processing may serve as a risk factor for the development of comorbid depression in ASD (Chapter 6). Using an affective preferential viewing task, modified from our original social/nonsocial preferential viewing task, I observed similar patterns of visual attention between adults with ASD and those with major depressive disorder. I further observed a relationship between two independent, reward-related diagnostic constructs: intensity of circumscribed interests and severity of ruminative thought, suggesting that altered reward in ASD may confer risk for co-occurring neuropsychiatric diagnoses.

Importantly, results of these studies emphasize *enhanced* reward in autism for nonsocial information, but not necessarily deficient response to social reward. Rather, reward seeking in autism may be context-dependent, such that social approach may be relatively intact, but is diminished or detracted from in the presence of something that is perhaps more highly salient. These studies further suggest that nonsocial reward is enhanced, compared to typical development, at two time points when social information may be particularly salient: at early developmental levels *and* during adolescence / adulthood. Future research that focuses on understanding the full developmental trajectory of altered reward in ASD will benefit targeted therapeutic interventions that are specific to typical developmental stages (e.g., How do social and nonsocial reward interact during early language-sensitive developmental periods or during later childhood / adolescence when social isolation can increase the risk for depression and anxiety?).

Reward as an endophenotype in ASD

The dynamic motivation model of ASD presents a conceptual shift, from characterization of symptom profile, to consideration of contributing mechanism. The primary value of symptom-based language is in determining how diagnostic states differ from one another. Explicit symptom profiles facilitate correct differential diagnosis, allowing for specificity of treatment. Indeed, without proper characterization of ASD-specific symptomology, this diagnosis may become confused with similar, but unique diagnoses. For example, a gold-standard autism screening measure should show specificity to this diagnosis, such that a child with obsessive compulsive disorder does not score within diagnostic range. In this way, symptom-based, or disorder-specific language is utilized to create distinctions between behaviors that may appear phenotypically similar.

The use of within-disorder measurement tools may give the false impression that phenotypically similar behaviors are unique phenomena, when in reality, these similarities may indicate common mechanisms or pathophysiology. Such commonalities, particularly within neuropsychiatric research, suggest that efforts toward models of therapeutic intervention may be optimized through cross-diagnostic research. This consideration may be particularly relevant for idiopathic ASD, which has no known genetic pathway; rather, genes implicated in autism are common to many neuropsychiatric disorders (Viding & Blakemore, 2007). Yet, current methods of classification within neuropsychiatry are not based on underlying genetic or biological pathophysiology (Gottesman & Gould, 2003). Therefore, existing tools (i.e. primarily disorder-specific measures) limit generalizability across diagnostic groups.

Endophenotypes are "measureable components, unseen by the unaided eye that lie along the pathway between disease and distal genotype" (Gottesman & Gould, 2003). The non-specificity of endophenotypes allows for cross-diagnostic measurement because they are not bound by symptom-specific language. An ultimate goal of endophenotypes within autism research is to reduce the vast heterogeneity that is observed in both phenotypic presentation and genetic predisposition (Viding & Blakemore, 2007). Importantly, an endophenotype doesn't confer diagnostic status. Rather, an endophenotype is a reliable and persistent trait that is associated with the symptom profile of interest and its potential causal mechanisms and shows evidence for genetic heritability (Gottesman & Gould, 2003). Therefore, a given endophenotype may be common across *multiple* neuropsychiatric diagnoses and evident in unaffected individuals (although likely more common in family members of affected individuals).

Alterations in functional reward circuitry are common to many neuropsychiatric diagnoses (e.g., Whitton, Treadway, & Pizzagalli, 2015; Yacubian & Büchel, 2009), including those with which autism shares genetic susceptibility (Geschwind, 2008). The studies here provide converging evidence with existing literature in support of reward processing as an endophenotype in ASD and for the LPP as a potential dimensional and sensitive neural marker of this reward endophenotype. Further, the expression of the reward endophenotype that appears to be specific to ASD may be a pattern of responding in reward-related tasks characterized by atypical or enhanced responses to nonsocial reward. This conceptualization of reward as an endophenotype in ASD could guide future research by focusing on potential commonalities across differing neurodevelopmental and neuropsychiatric conditions to identify shared pathophysiology and to explore novel approaches for the development of therapeutic interventions.

Relating the reward endophenotype to models of brain structure and function in ASD

Studies examining the neurobiological basis of autism are frequently limited in interpretability due to a lack of association between underlying brain differences and overt behavioral phenotype. Symptom-based measures may present specific confounds in limiting variability to establish such relationships. However, focusing on endophenotypes of ASD, such as alterations in reward, may provide the necessary "bridge" between these two levels of measurement. This both allows direct comparisons to be made about mechanistic underpinnings of behavioral differences and promotes increased understanding across disorders, rather than restricting research within them.

It is important to consider a potential reward endophenotype in relation to what is known about brain structure and function in ASD. One candidate mechanism in this regard is the salience network. A recent study of large-scale brain networks in ASD found that alterations in the salience network were most effective in classifying ASD group membership (Uddin et al., 2013). The salience network has been hypothesized to play a key role in orienting attention toward salient events based on its unique position to integrate neural information from both physiological (e.g., hypothalamus, amygdala) and motor-related (e.g., substantia nigra, anterior cingulate cortex) regions of the brain (Menon & Uddin, 2010; Uddin, 2015). Therefore, one probable consequence of altered functional connectivity of the salience network is aberrant detection of salient stimuli. The insula is a primary node of the salience network, and may play a critical role in helping an individual to detect and allocate attention to relevant salient stimuli (e.g., Hahn, Ross, & Stein, 2006), communicating this information to other network nodes (e.g.,

anterior cingulate cortex) to adjust and coordinate task-relevant responses (e.g., motor output). Both alterations in the salience network and insular dysfunction have been shown to be related to repetitive behavior (Uddin et al., 2013) and nonsocial reward (Cascio et al., 2014) in ASD. Therefore, it is reasonable to hypothesize that altered function of the salience network in ASD may lead to enhanced nonsocial reward through cascading effects of abnormal salience attribution toward specific types of stimuli.

Clinical implications of the reward endophenotype model of ASD

Improving early identification, and therefore early intervention, is a priority within the field of autism. The current average age of diagnosis is approximately 4 years (Christensen, 2016), with consensus agreement of stable diagnoses being given as young as 24 months of age (Lord et al., 2006). One primary limitation of early identification of autism is the lack of specificity of early "signs" of autism, from other developmental disorders. Diagnosis of ASD is also critically dependent upon the presence of delayed social use of communication, including spoken language. Due to its very nature, this marker cannot be translated into earlier time points. Translation of early identification methods from symptom to mechanism-focused indices may help to overcome such barriers. Reward-related behaviors such as orientation, preference, and choice can be reliably measured in infancy and thus may provide a set of risk markers that could be identified earlier in development than conventional, diagnosis-based, behavioral methods. Further, EEG metrics, like the LPP, can also be reliably measured in early childhood and can provide a means for identifying early neural differences in the relative salience of social and nonsocial sources of stimulation.

Implications for future research

The studies present here provide a framework within which to consider reward alterations in the context of ASD. In order to further establish reward as an endophenotype in ASD, I suggest two avenues of future research. First, it is critical to establish longitudinal developmental trajectories of reward function in ASD. Although it can be hypothesized that functional alterations in reward are present in ASD very early in development, the manifestation of these alterations may differ across development. This is particularly relevant given changes in reward functioning that are associated with typical development (e.g., Galvan, 2010). Similarly, the implications of altered reward may differ across the lifespan, potentially conferring risk for language delay early in life and depression during adolescence and adulthood. Further, psychometrically sound ways of measuring reward-related alterations likely also differ across development. For example, nonsocial approach may be reflected as increased object engagement during infancy (Maestro et al., 2002, 2005; Osterling, Dawson, & Munson, 2002; Ozonoff et al., 2008), while measurement of individual interests may better reflect this construct in adolescence (e.g., Cascio et al., 2014).

A second avenue for future research is to parse the neurogenetic basis of the reward endophenotype in ASD, guided by the Research Domain Criteria (RDoC), as proposed by the National Institute of Mental Health. The Positive Valence Systems domain of the RDoC matrix is comprised of multiple facets of reward processing, including approach motivation, reward learning, habit, and temporal responsivity to reward attainment, each of which may contribute differentially to the reward endophenotype in ASD. Establishing profiles of function across each of these mechanism-based constructs may highlight pathophysiological alterations and / or narrow the vast molecular contributions into more managable targets for etiological and

treatment-based studies. Recent research outside of ASD has begun to elucidate the contribution of dopaminergic genetic variants to variability in reward processing across neurotypical / healthy individuals (Bogdan, Nikolova, & Pizzagalli, 2013). For example, differing receptors regulate dopamine in the striatum, compared to the cortex, meaning that each of these may be expressed differently across the brain, based on an individual's specific profile of alleles. Therefore, rather than identifying one specific locus that confers risk for reward-based alterations, this research approach may help to identify specific combinations of normally occurring variants that contribute to this endophenotype. Finally, this line of research may contribute to the design of mechanistically valid translational models, providing a more direct target for studies of therapeutic intervention.

Summary and conclusion

Reward is a dynamic process by which an individual's internal physiology, external environment, and previous experiences interact to guide current and future patterns of behavior. Therefore, reward responsivity may vary greatly, given the context in which it is presented, and an individual's cumulative and unique experiences. The purpose of this dissertation was to develop a model that reframes autism through the perspective of a dynamic model of reward, and to provide tests of this model. Taken together, the studies presented here provide empirical evidence that nonsocial reward is enhanced in ASD and may impair engagement with social information, despite intact responses to social reward. More broadly, these studies suggest that distinct aspects of the autism phenotype may be related to a common underlying mechanism. The conceptual shift from a symptom-based model provides a framework in which to examine the influence of reward processing across multiple aspects of the autism phenotype, and links

functional alterations in brain reward circuitry to the expression of a variety of behavioral, affective, and cognitive symptoms that make up the autism phenotype.

REFERENCES

Bogdan, R., Nikolova, Y. S., & Pizzagalli, D. A. (2013). Neurogenetics of depression: a focus on reward processing and stress sensitivity. *Neurobiology of Disease*, *52*, 12–23.

Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P., … Cao, A. (2014). Affective neural response to restricted interests in autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*(2), 162–171.

Christensen, D. L. (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR. Surveillance Summaries*, *65*. https://doi.org/10.15585/mmwr.ss6503a1

Galvan, A. (2010). Adolescent development of the reward system. *Frontiers in Human Neuroscience*, *4*, 116–124.

Geschwind, D. H. (2008). Autism: many genes, common pathways? *Cell*, *135*(3), 391–395.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *The American Journal of Psychiatry*, *160*(4), 636–645. https://doi.org/10.1176/appi.ajp.160.4.636

Hahn, B., Ross, T. J., & Stein, E. A. (2006). Neuroanatomical dissociation between bottom-up and top-down processes of visuospatial selective attention. *NeuroImage*, *32*(2), 842. https://doi.org/10.1016/j.neuroimage.2006.04.177

Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., & Pickles, A. (2006). Autism from 2 to 9 years of age. *Archives of General Psychiatry*, *63*(6), 694–701.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., … Menon, V. (2013). Salience network–based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry*, *70*(8), 869–879.

Viding, E., & Blakemore, S.-J. (2007). Endophenotype approach to developmental psychopathology: implications for autism research. *Behavior Genetics*, *37*(1), 51–60.

Whitton, A. E., Treadway, M. T., & Pizzagalli, D. A. (2015). Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry*, *28*(1), 7.

Yacubian, J., & Büchel, C. (2009). The genetic basis of individual differences in reward processing and the link to addictive behavior and social cognition. *Neuroscience*, *164*(1), 55–71.