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Investigations of Attention in Autism Spectrum Disorder: Are Anomalies in Attention Related to the Development of Sociocommunicative Impairments?

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Language and Communicative Disorders

by

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BOOK CHAPTERS

Townsend, J., **Keehn, B.**, & Westerfield, M. (in press). "Abstraction of mind": Attention in autism. In M. Posner (Ed.), *Cognitive Neuroscience of Attention*: Guilford Press

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Keehn, B., Shih, P., Nair, A., Khan, A., Westerfield, M., Lincoln, A.J., Townsend, J., & Müller, R-A. (2011, May). Attentional Capture in ASD: A Combined fMRI-EEG Study. Poster presented at the International Meeting for Autism Research, San Diego, CA.

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Keehn, B., Lincoln, A.J., Müller, R-A., & Townsend, J. (2009, May). A study of attentional networks in individuals with autism spectrum disorder. Poster presented at the International Meeting for Autism Research, Chicago, IL.

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Shukla, D.K., **Keehn, B.**, Lincoln, A.J., & Müller, R-A. (2009, May). Probabilistic DTI tractography shows compromised connectivity between regions of atypically increased activity in children with autism spectrum disorder. Paper presented at the International Meeting for Autism Research, Chicago, IL.

Jensen, B., **Keehn, B**., Brenner, L.A., Lincoln, A.J., Marshall, S.P., & Müller, R-A. (2009, May). Increased eye-blink rate in autism spectrum disorder may reflect dopaminergic abnormalities. Poster presented at the International Meeting for Autism Research, Chicago, IL.

Shen, M., Gaffrey, M., **Keehn, B**., Villalobos, M., Shukla, D., & Müller, R-A. (2008, November). Functional connectivity of extrastriate cortex in autism: An fcMRI study of semantic decision. Paper presented at Neuroscience, Washington D.C.

Shukla, D.K., **Keehn**, **B**., Brenner, L.A., & Müller, R-A. (2008, November). Regional homogeneity of fMRI activation in autism. Poster presented at Neuroscience, Washington D.C.

Keehn, B., Brenner, L.A., Palmer, E., Lincoln, A.J., & Müller, R-A. (2008, May). fMRI investigation of visual search in autism spectrum disorder. Paper presented at the International Meeting for Autism Research. London, England.

DiNino, S., **Keehn, B**., Brenner, L.A., Lincoln, A.J., Marshall, S.P., & Müller, R-A. (2008, May). Enhanced performance on the Embedded Figures Test in autism is not linked to cognitive effort: A pupil dilation study. Poster presented at the International Meeting for Autism Research. London, England.

Sanchez, S., **Keehn, B**., Brenner, L.A., Marshall, S.P., & Müller, R-A. (2008, May). Oculomotor correlates of enhanced visual search in autism spectrum disorder: A study of binocular coordination. Paper presented at the International Meeting for Autism Research. London, England.

Shukla, D.K., **Keehn**, **B**., Grenesko, E.L., Shen, M., Lincoln, A.J., & Müller, R-A. (2008, May). White matter integrity in patients with autism spectrum disorders. Poster presented at the International Meeting for Autism Research. London, England.

Keehn, B., Brenner, L.A., Ramos, A.I., Lincoln, A.J., Marshall, S.P., & Müller, R-A. (2007, November). An eye-tracking investigation of embedded figures performance in individuals with autism. Poster presented at Neuroscience, San Diego, CA.

Horowitz, T.S., Wolfe, J.M., **Keehn, B**., Connolly, C., & Joseph, R.M. (2007, May). Is superior visual search in autism due to memory in search? Poster presented at the Vision Sciences Society, Sarasota, FL.

Keehn, B., Fine, A., Connolly, C., & Joseph, R.M. (2007, May). Slowed visual search in the absence of top-down information in autism. Poster presented at International Meeting for Autism Research, Seattle, WA.

Keehn, B., Fine, A., Connolly, C., & Joseph, R.M. (2007, April). Bottom-up modulation of attention in autism: A visual search experiment. Poster presented at biennial meeting of the Society for Research in Child Development, Boston, MA.

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ABSTRACT OF THE DISSERTATION

Investigations of Attention in Autism Spectrum Disorder:
Are Anomalies in Attention Related to the Development of Sociocommunicative Impairments?

by

Brandon Michael Keehn

Doctor of Philosophy in Language and Communicative Disorders

University of California, San Diego, 2011
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Professor Ralph-Axel Müller, Co-Chair
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While a diagnosis of autism spectrum disorder (ASD) is based on impairments and anomalies in the domains of communication, reciprocal social interaction, and restricted and repetitive behaviors, *attentional abnormalities* have been considered an associated feature of the disorder since it was originally described. Prior research, reviewed in Chapter 1, has demonstrated that individuals with ASD exhibit early and pervasive impairments in the adaptive allocation of attention. The ubiquitous nature of attentional dysfunction in ASD has prompted the hypothesis that aberrant attentional modulation may act as a significant contributing factor in the development of higher-level sociocommunicative deficits. The

objective of the studies presented in this dissertation was to further elucidate patterns of attentional strengths and weaknesses in ASD and to examine whether atypical attentional processes are related to core ASD deficits in social and communication functions.

The study presented in Chapter 2 employs behavioral and eye-tracking measures to investigate novelty processing in ASD, and, furthermore, examines how sensitivity to new information is related to sociocommunicative impairments in ASD. Chapter 3 presents an investigation of three attentional networks (alerting, orienting, and executive control) and how efficiency of each attentional network is associated with ASD symptomatology. Chapters 4 and 5 present functional magnetic resonance imaging (fMRI) studies of activation and connectivity of attentional networks associated with visual search in ASD, and how behavioral and neural indices of search are related to deficits in social and communicative abilities.

Together, results from these studies provide further evidence of atypical attention function in ASD. Moreover, findings from these chapters demonstrate that decreased sensitivity to new information (Chapter 2), reduced alerting efficiency (Chapter 3), and increased search efficiency (Chapter 5) are related to increased symptom severity in children and adolescents with ASD. A preliminary framework for understanding the distinct pattern of attentional strengths and weaknesses, and how these may be related to the development of the triad of impairments and anomalies used to define ASD is outlined. Lastly, potential avenues for future research and possible treatment implications based on the results and conclusions are discussed.

CHAPTER 1

Introduction

Attention can be defined as information processing mechanisms that mediate perceptual selectivity. It is as James put it, "the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneous possible objects or trains of thought" (James, 1890, pp. 403-404). From birth we are inundated on a moment-by-moment basis with an abundance of both internal and external stimuli. Attentional subsystems are responsible for the adaptive allocation of limited capacity brain resources in order to efficiently process, select, and respond to this incoming information. Attentional selection is controlled by endogenous, goal-directed mechanisms dependent on the desires, expectations, and/or knowledge of the observer (i.e. top-down control) and exogenous, stimulus-driven (bottom-up) factors strictly defined as orthogonal to goal-directed behaviors (Yantis, 1993) and loosely defined as dependent on the physical characteristics of the stimuli (Wolfe, 1994). Attentional selection rarely consists of exclusively top-down or bottom-up mechanisms; rather, successful and adaptive information processing requires the integration of these two processes (see Pashler, Johnston, & Ruthruff, 2001, for review). Selection may occur early with irrelevant information filtered from further processing or late with irrelevant information processed to a greater degree (see Pashler, 1999, for review) and is dependent on the perceptual load of the stimuli to be processed (Lavie, 2005). Furthermore, subcomponents of attention follow unique developmental trajectories (see Enns, 1990; Ruff & Rothbart, 1996, for review), interacting in a multidirectional manner with other attentional subsystems, gene expression, and brain maturation across development (M. H. Johnson, 2011).

Attentional subsystems and the neural substrates associated with these functions may operate as *domain-relevant* mechanisms (Karmiloff-Smith, 1998) for later developing higher-level sociocommunicative functions. An example of this, as previous described by Karmiloff-

Smith (2009), is the role of impaired oculomotor control in the development of language abilities in infants and toddlers with Williams syndrome. She has hypothesized that a dysfunctional saccade planning system results in subsequent deficits in following pointing that, in turn, results in the limited use of parent referential pointing to acquire new words. Ultimately, in conjunction with other contributing factors, this leads to delayed language abilities in children with Williams syndrome. The timing of this initial deficit is as important as the deficit itself; therefore understanding the developmental time course of anomalies in attentional processes is vital to understanding how these impairments may affect the development of higher-level cognitive functions. Furthermore, understanding neurofunctional bases of these attentional subsystems and their development may also facilitate an understanding of both typical and atypical specialization of these attentional networks (M. H. Johnson, Halit, Grice, & Karmiloff-Smith, 2002). Because the adaptive allocation of attention is essential for perceiving and interacting with our environment, understanding both typical and atypical brain and behavioral development of these attentional functions may have important significance for developmental disorders that are associated with attentional deficits. This knowledge will provide insight as to whether these disorders are the result of domain-specific impairments to unique higher-level functions, or whether early impairments in attention result in a cascade of processing deficits (and strengths).

The most recent estimation indicates that one in every 110 children is diagnosed with autism spectrum disorder (ASD) (CDC, 2009), with a higher incidence in males as compared to females (3:1-4:1) (Folstein & Rosen-Sheidley, 2001). Autism spectrum disorder is a behaviorally-defined disorder diagnosed on the basis of impairments and anomalies in the domains of communication, reciprocal social interaction, and repetitive and stereotyped behaviors (APA, 2000). While a diagnosis of ASD is based on this triad of features, *attentional abnormalities* have been associated with the disorder since its first description

(Kanner, 1943). Individuals with ASD exhibit early (Baranek, 1999; J. Brian et al., 2008; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson et al., 2004; Elsabbagh et al., 2009; Garon et al., 2009; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002; Swettenham et al., 1998; Zwaigenbaum et al., 2005) and pervasive (see Allen & Courchesne, 2001; Burack, Enns, Stauder, Mottron, & Randolph, 1997, for review) impairments in attention. The ubiquitous nature of attentional dysfunction in ASD has led investigators to hypothesize that early atypical attentional modulation may act as a significant contributing factor in the development of higher-level sociocommunicative deficits (Belmonte & Yurgelun-Todd, 2003; Courchesne, Townsend, Akshoomoff, Yeung-Courchesne et al., 1994; Dawson & Lewy, 1989; Gold & Gold, 1975; Ornitz, 1988; Pierce, Glad, & Schreibman, 1997). Therefore, understanding the development of attentional mechanisms in children with ASD could help to elucidate the abnormal or delayed trajectories of attentional development, and further, how these attentional abnormalities may contribute to the manifestation of the core ASD symptomatology.

In this chapter, I will introduce a theoretical framework of the attentional subsystems previously proposed by Posner and Petersen (1990) and review the experimental literature relevant to the development of these systems in typically developing (TD) individuals. Next, I will review the extant literature on attention in ASD within the context of these attentional subsystems. Finally, I will discuss research investigating the relationship between non-social attentional processes and the development of sociocommunicative functioning and then review findings linking attentional impairments to higher-level sociocommunicative dysfunction in ASD. This will be the theoretical and empirical foundation for the experimental studies presented in Chapters 2 – 5. Lastly, Chapter 6 will integrate the findings from these studies and attempt to put forth a hypothesis regarding how aberrant attentional mechanisms may function as an etiological agent with regard to core ASD symptomatology.

Attention Networks

Despite the often cited edict that "everyone knows what attention is" (James, 1890, p. 403), researchers have proposed a variety of theories of attention and models outlining the functions of attentional subcomponents, suggesting that a debate regarding the dissociable components of attention and their neurofunctional underpinnings remains. However, these models of attention and their associated attentional subcomponents exist with varying degrees of overlap. Posner and Petersen (1990) have proposed a model that divides attention into three independent, but interacting networks: alerting, orienting, and executive control. More recently, Corbetta and colleagues (2008; 2002) have outlined a separate but overlapping model that divides attention into two neuroanatomical networks: the dorsal (similar to orienting) and ventral (similar to alerting) fronto-parietal networks. These networks, their typical development, and their function in individuals with ASD, will be reviewed below.

Alerting Network

The alerting network is responsible for achieving and maintaining a state of increased sensitivity to incoming information. Alertness has been divided into tonic and phasic subcomponents (see Sturm & Willmes, 2001, for review), which may interact to increase or decrease information processing capacity (Kahneman, 1973) and influence the breadth of selective attention (Easterbrook, 1959). Tonic alertness is a state of general wakefulness; endogenously-controlled tonic alertness (referred to as vigilance or sustained attention) is the voluntary maintenance of alertness at a certain level. Phasic alertness is a more transient alert state, commonly modified by a warning that precedes a target stimulus. These components of alertness parallel the tonic and phasic attributes of Sokolov's orienting response (OR) theory (Sokolov, 1963).

Briefly, there are two additional interrelated mechanisms associated with alerting that should be addressed: novelty detection and habituation. Novelty detection is a fundamental

characteristic of Sokolov's OR (1963), and is dependent on a stimulus mismatch between an individual's pre-existing representation and a novel stimulus; a phasic OR does not take place without the perception of a novel stimulus. It is therefore an important prerequisite for an OR, which subsequently enables an individual to encode and process novel environmental information. Habituation is the decline of the OR due to stimulus repetition. The degree to which an individual perceives information to be novel (by discriminating between old and new stimuli) will affect the presence and scale of an alerting response. Thus, the rate at which an individual habituates (or does not habituate) to a given stimulus will also affect the level of alertness at any given stimulus repetition.

The cortical brain network underlying alerting function includes right lateralized frontal and parietal regions (Posner & Petersen, 1990). In general, these regions overlap with the ventral fronto-parietal network proposed by Corbetta et al. (Corbetta et al., 2008; Corbetta & Shulman, 2002), which serves as an alerting system and may be the source of a 'circuit breaker' mechanism that is responsible for reorienting attention to behaviorally-relevant stimuli (to a separate 'attentional set' rather than spatial location). Also included within the functional neuroanatomy of the alerting network in both models is the locus coeruleus - norepinephrine (LC-NE) system, which is the core arousal center in the brain (see Robbins & Everitt, 1995, for review). In general, the LC-NE system supports appropriate levels of alertness in order maintain efficient information processing.

Alerting function in typical development. The development of tonic alertness and the waking state in infants shifts rapidly between 2 and 24 weeks (Dittrichova & Lapackova, 1964). Early infant attention functions to maintain a state of homeostasis and is highly dependent on the level of internal arousal and the amount of external stimulation (Karmel, Gardner, & Magnano, 1991).

A technique widely used to examine attentional modulation in neonates and infants is directional heart rate (HR) response (see Richards & Casey, 1992, for review). Stimulus orienting (a measure of phasic OR discussed above) consists of a large post-stimulus deceleration lasting approximately five seconds; during this phase, evaluation of novelty and preliminary processing of stimulus characteristics take place. The subsequent stage, sustained attention, is the endogenous maintenance of the original OR (continued HR deceleration) for purposes of more detailed information processing and lasts between two and twenty seconds, depending on the state of the infant and the novelty and complexity of the stimulus. This phase has been described as a 'non-specific arousal system' that reduces distractibility (Richards & Casey, 1992). In general, the magnitude of HR decelerations associated with the OR increases with age (see Reynolds & Richards, 2008, for review). No significant developmental changes occur for the stimulus orienting phase in 14, 20, and 26 week-old infants, however, sustained attention abilities undergo a more protracted developmental time course, increasing rapidly from 2 to 6 months (see Richards, 1995, for discussion).

The development of endogenous control of tonic alertness (sustained attention) from childhood to adolescence has often been measured using Continuous Performance Tests (CPT). In a CPT, participants are asked to respond to a predefined target stimulus presented randomly among streams of non-target stimuli. Endogenous control of tonic alertness, as measured by the CPT, increases significantly from 3 to 6 years of age (Akshoomoff, 2002; Kerns & Rondeau, 1998; Levy, 1980) and continues to develop into late childhood and adolescence, reaching adult-like levels around the age of 12 years (Lin, Hsiao, & Chen, 1999). Phasic alertness develops more rapidly, continuing to develop between 5 to 8 years of age, but reaching adult-like levels at approximately 8 years old (Morrison, 1982).

Recently, Fan and colleagues (2002) developed the Attention Network Test (ANT) to examine the efficiency of each attentional network. The ANT consists of both a cued reaction

time task (Posner, 1980) and a flanker paradigm (Eriksen & Eriksen, 1974), and is a measure of both phasic and tonic components of alertness (Posner, 2008). Results from cross-sectional studies suggest that alerting efficiency may increase from 4 to 7 years of age (Mezzacappa, 2004). A separate study indicated that while the efficiency of the alerting network may not change between 6 and 9 years, 10-year-old children do show significantly reduced alerting efficiency as compared to adults (Rueda et al., 2004). These developmental changes in alerting efficiency between 10-year-old children and adults, as measured by the ANT, are likely due to changes in the level of tonic alertness. Neuroimaging findings from an fMRI study of the ANT (Konrad et al., 2005) revealed that children (mean age = 10.1 years) recruited right middle occipital cortex extending to superior temporal gyrus, while adults (mean age = 26.6 years) recruited right ventral prefrontal cortex, left superior parietal lobe, and cerebellum. Additionally, adults exhibited greater activation in midbrain and anterior cingulate gyrus. These results suggest that networks mediating both phasic and tonic levels of alertness may not be fully developed by the age of 10.

The development of alerting mechanisms has also been investigated using event-related potentials (ERPs). One example is the Nc (negative central) component (Courchesne, 1977, 1978), which occurs between 350-800ms post-stimulus onset at central electrode sites. This component has been hypothesized to represent an OR that is insensitive to novelty and stimulus probability (Nelson & Collins, 1992; Richards, 2003). It appears that in the first year of life during attentive states the amplitude of the Nc component increases, while the latency decreases (Richards, 2003). The amplitude of the Nc component decreases significantly from 6 to 8 years of age through adolescence as the electrophysiological response transitions to the more mature P3 waveform (Courchesne, 1978).

As discussed above, an important factor in the modulation of alertness is novelty detection. One electrophysiological index of novelty processing, usually elicited with an odd-

ball paradigm (analogous to the CPT), is the modality-independent P3 component (see Polich, 2007, for review). Briefly, the P3 component consists of two subcomponents: 1) a frontocentral P3a (novelty P300) component that habituates rapidly and is associated with the redirection of attention monitoring during stimulus discrimination, and 2) a parietal P3b component that reflects a memory comparison and facilitates context maintenance. Previous research has demonstrated that these components reflect activity of separate neural generators and neurotransmitter systems (Polich, 2007) and involve regions such as the temporal-parietal junction, lateral prefrontal cortex, and the LC-NE system (see Nieuwenhuis, Aston-Jones, & Cohen, 2005, for discussion). Developmental changes associated with the P3 component include decreased latency (Courchesne, 1978; Zenker & Barajas, 1999) and changes in scalp amplitude distribution, specifically, increased amplitude over frontal electrode sites (Courchesne, 1978). Increased amplitude of the frontal component (especially for novel stimuli) in adults may reflect the development of a new frontal P3 generator.

The alerting network develops rapidly during the first year of life. Physiological indices (HR, ERP) demonstrate early development of the system responsible for non-spatial orienting to new information. The efficiency and speed of phasic alerting may continue to develop into the early school-age years (Morrison, 1982), while endogenous maintenance of alertness (sustained attention) has a more protracted course of development, not reaching adult-like levels until early adolescence (Lin et al., 1999).

Alerting function in ASD. Levels of tonic arousal and the modulation of phasic alertness have been areas of intense speculation and modest empirical consensus in ASD-related research (see Bryson, Wainwright-Sharp, & Smith, 1990; Rogers & Ozonoff, 2005, for review). Previous authors have argued that individuals with ASD exhibit hyperarousal (Hutt, Hutt, Lee, & Ounsted, 1964), hypoarousal (Rimland, 1964), and dysfunctional arousal modulation (Ornitz & Ritvo, 1976). Others (van Engeland, 1984) have proposed that

"nonresponsiveness" (i.e. hypoarousal) may develop as a result of sensory overload due to early chronic hyperarousal. Furthermore, Liss and colleagues (2006) hypothesize that hyperarousal in ASD may lead to the development of overselective attention, and, similar to van Engeland (1984), that this may result in reduced or absent OR to stimuli that may be outside an atypically narrower focus of attention. Additionally, varying theoretically- and empirically-driven hypotheses and the inconsistency of previous findings of hypo- and hyperarousal may be the result of separate subgroups of children with ASD that exhibit one of the two arousal states (Hirstein, Iversen, & Ramachandran, 2001; Schoen, Miller, Brett-Green, & Hepburn, 2008).

Evidence for hyperarousal in ASD comes from prior research which has demonstrated increased overall skin conductance levels (SCL) and increased number of skin conductance responses (SCR) and a decreased HR deceleration (or a relative acceleration) (Palkovitz & Wiesenfeld, 1980), increased baseline HR (Ming, Julu, Brimacombe, Connor, & Daniels, 2005), and significantly larger tonic pupil size (Anderson & Colombo, 2009) in ASD as compared to non-autistic comparison groups.

Contrary to evidence of hyperarousal in ASD, equivalent or reduced levels of arousal have also been shown. Prior studies have reported no differences between low-functioning children and adolescents with ASD and CA- and MA-matched TD individuals in electrodermal response to an auditory habituation paradigm (Stevens & Gruzelier, 1984). Equivalent SCL, spontaneous SCR, and HR during rest have also been shown in high-functioning adults with ASD compared to TD individuals (Zahn, Rumsey, & Van Kammen, 1987). In addition, a previous study has also demonstrated no difference in spontaneous fluctuations in skin conductance to auditory stimuli between ASD, TD, and developmentally delayed (DD) children (van Engeland, 1984). Interestingly, van Engeland (1984) interpreted the findings in a high-functioning subgroup (IQ > 80) to represent a "paradoxical reaction," in

which participants were atypically open to environmental stimuli, and thus, potentially overwhelmed with sensory information. The results of the atypically increased openness to sensory information may lead to previously discussed hyperaroused states, and subsequently, to the development of sensory non-responsiveness to novel stimuli. In support of this hypothesis, van England and colleagues (1991) demonstrated that high-functioning children with ASD evidenced significantly reduced SCR and fixation times to novel visual stimuli. These findings highlight the importance of tracking the development of these attentional functions, which may not be static across development.

In addition to evidence of both hyper- and hypoarousal, impaired modulation of arousal between rest and task states may also be characteristic of ASD. Prior research has shown that individuals with ASD evidence reduced responsiveness in HR variability between rest and task states (Althaus, Mulder, Mulder, Aarnoudse, & Minderaa, 1999; Toichi & Kamio, 2003), reduced reactivity for task versus baseline, and decreased phasic SCR activity to imperative stimuli in a simple RT-task (Zahn et al., 1987). These findings are thought to be indicative of dysfunctional modulation of arousal in ASD.

Vigilance or sustained attention has been examined in ASD using the CPT (previously discussed). Prior studies have demonstrated intact sustained attention abilities (Garretson, Fein, & Waterhouse, 1990; Noterdaeme, Amorosa, Mildenberger, Sitter, & Minow, 2001; Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998). More recently, Johnson and colleagues (2007) reported that errors of omission and RT patterns were equivalent in ASD and TD participants on a modified version of the CPT. These findings suggest that endogenous maintenance of tonic alertness in ASD may function similar to TD individuals.

Behavioral evidence also suggests equivalent phasic alerting in ASD. Raymaekers and colleagues (2006) measured RT to a visual target that was and was not preceded by an auditory cue in a group of high-functioning children with ASD and age- and IQ-matched TD

individuals. Results indicated that both groups evidenced a similar RT-advantage to targets appearing after cues, and suggest that modulation of phasic alertness to auditory cues may be intact in children with ASD. However, electrophysiological measures of phasic alerting have demonstrated impaired function in ASD. The N1c component, which may reflect automatic attentional capture, is reduced in children with ASD (Bruneau, Bonnet-Brilhault, Gomot, Adrien, & Barthelemy, 2003; Orekhova et al., 2009). Additionally, prior studies have also demonstrated reduced Nc amplitude in adolescents and adults with ASD (Ciesielski, Courchesne, & Elmasian, 1990; Courchesne, Lincoln, Kilman, & Galambos, 1985). More recently, McCleery and colleagues (2009) reported reduced Nc amplitudes in 10-month-old infants at risk for ASD compared to TD infants during passive viewing of faces and objects.

Novelty detection has been a large focus in previous investigations of attention in ASD. Prior behavioral evidence suggests that children with ASD may be insensitive to the onset of new information (Greenaway & Plaisted, 2005). Moreover, multiple studies have revealed reduced P3 amplitude (discussed above) in response to novel target auditory (Ciesielski et al., 1990; Courchesne, Kilman, Galambos, & Lincoln, 1984; Courchesne et al., 1985; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Dawson, Finley, Phillips, Galpert, & Lewy, 1988; Lincoln, Courchesne, Harms, & Allen, 1993; Novick, Kurtzberg, & Vaughn, 1979; Novick, Vaughan, Kurtzberg, & Simson, 1980) and visual targets (Ciesielski et al., 1990; Courchesne et al., 1989; Pritchard, Raz, & August, 1987; Townsend et al., 2001) in ASD. A separate electrophysiological index of novelty detection, mismatch negativity (MMN), has also been examined in ASD. MMN is elicited when a novel/deviant auditory stimuli is presented within a stream of repetitive standard stimuli. Findings from studies investigating MMN in ASD have been mixed (see Bomba & Pang, 2004, for review). More recently, Dunn et al. (2008) examined MMN in ASD and TD children during both passive and active listening conditions. The authors report that, in

passive listening conditions, children with ASD showed reduced MMN amplitude compared to their TD peers; however, no difference in MMN amplitude was found when participants were instructed to actively discriminate auditory stimuli. The authors conclude that *automatic* auditory processing is dysfunctional in ASD.

Recently, Gomot and colleagues (2008; 2006) examined passive and active detection of auditory oddball stimuli using fMRI. Passive detection of novel auditory stimuli resulted in greater activation in bilateral temporal-parietal junction and right inferior and middle frontal regions in the TD compared to ASD group. In contrast, activation for active novelty detection was significantly greater in the right prefrontal cortex and left inferior parietal lobule in the ASD compared to the TD group. Thus, atypical activation to novel stimuli may be dependent on the context of the experiment. Reduced ASD activation (and reduced MMN amplitude) for passive novelty detection may result from a predisposition to ignore novel information. However, Gomot et al. suggest that increased ASD activation to active novel detection may reflect over-focusing in the ASD group, which could result in maladaptive allocation of attention. Critically, the differential response to novelty in ASD may reflect task- or context-dependent attentional states.

Mixed results have been observed in studies investigating tonic levels and phasic responsiveness of the alerting network in ASD, and limit unequivocal conclusions regarding dysfunction within this attentional network. The alerting network reflects a complicated interaction between the internal state of the individual, their responsiveness to external stimuli, and their task- or goal-related endogenous modulation of alertness. Therefore, elucidating underlying alerting abnormalities in ASD has proven difficult. Further complicating the study of the alerting network is the fact there may be separate subgroups of hyper- and hypoaroused individuals with ASD. In sum, previous evidence has demonstrated increased plasma-levels of norepinephrine (see Lam, Aman, & Arnold, 2006, for review), increased pupil diameter,

aberrant skin conductance responses and levels, abnormal electrophysiological alerting response (Nc, N1c) and novelty detection (P3a, P3b), and atypical neurofunctional activation of the alerting network in persons with ASD. Although evidence of unimpaired phasic and endogenous tonic alertness exists, it seems that individuals with ASD do exhibit impairments in the alerting network.

Orienting Network

The orienting network is responsible for the selection of information from sensory input. Posner and colleagues (1984) have defined visuospatial orienting as disengaging, shifting, and reengaging attention. In contrast to the phasic alerting mechanisms that respond homogeneously across the visual field, orienting visual attention facilitates processing over a localized area and results in enhanced sensory responses (Mangun & Hillyard, 1991; Martinez et al., 2001).

However, it is important to note that while orienting cues generate spatial shifts in visual attention, they also alter the level of alertness of an individual (Hebb, 1949, as cited in Fernandez-Duque & Posner, 1997). Additionally, although anatomically distinct and functionally independent, alerting and orienting mechanisms do interact (Callejas, Lupianez, Funes, & Tudela, 2005; Callejas, Lupianez, & Tudela, 2004; Fan et al., 2009; Fuentes & Campoy, 2008). The results of Callejas et al. (2005) indicate that alerting accelerates orienting of attention to spatial locations. In addition, while phasic alertness modulates visuospatial orienting, the ability to disengage and shift attention during distressing situations may attenuate arousal levels (Derryberry & Rothbart, 1988). Thus, alerting (both phasic and tonic) may be bi-directionally related to orienting abilities.

Orienting visual attention can occur overtly, with concurrent head/eye-movements, or covertly, without simultaneous head/eye-movements. Additionally, attention may be directed reflexively (automatically) or voluntarily to a target location based on central (endogenous) or

peripheral (exogenous) cues. Finally, subsequent to reflexive cue-based attentional facilitation, RT to targets appearing at cued locations *increases* relative to non-cued locations. This process is referred to as inhibition of return (IOR; see Klein, 2000, for review) and reflects inhibition of previously searched locations and promotes orienting towards novel locations. Various indices of attentional orienting have been examined; RT or accuracy measures can be used to derive validity (invalid – valid), facilitation (neutral – valid), and cost effects (invalid – neutral) (although see Jonides & Mack, 1984, for discussion of caveats of cost and benefits).

The network of brain regions responsible for directing attention include superior parietal lobe, intraparietal sulcus, temporal-parietal junction and dorsofrontal (frontal eye fields) cortices, the thalamus, and superior colliculus (Corbetta & Shulman, 2002; Mesulam, 1990; Posner & Petersen, 1990). In addition, the cerebellum may also play a role in both covert and overt orienting of attention (Akshoomoff, Courchesne, & Townsend, 1997; Pelisson, Goffart, Guillaume, & Quinet, 2003).

Schiller (1985, 1998) has elegantly delineated the neural basis for overt control of attention. His model includes four pathways: two subcortical pathways involving the superior colliculus and anterior and posterior cortical pathways responsible for the execution of eye-movements. The superior colliculus receives visual input directly from the retina and from early visual cortex and transmits eye-movement vectors via the brainstem. The second collicular eye-movement pathway involves inhibitory connections from the substantia nigra via the basal ganglia and is responsible for the inhibition of eye-movements (IOR). The posterior cortical pathway receives visual information from higher extrastriate visual areas (area MT) and controls eye-movements via connections from the parietal lobe to subcortically controlled eye-movement centers. Both the superior colliculus and posterior networks are responsible for reflexive saccades. The final eye-movement pathway is the anterior system,

which includes visual information projected from the occipital, parietal, and temporal lobes and projects eye-movement information directly to the brainstem via the frontal eye fields, and is responsible for volitional control of eye-movements.

Orienting function in typical development. Johnson (1990) proposed a model of overt attention in infants based on the maturation of subcortico-cortical and cortico-cortical pathways as outlined by Schiller (1985; 1998; discussed above). Briefly, his model proposes that newborns use a functional superior colliculus pathway to mediate early reflexive shifts of attention. The development of the inhibitory pathway leads to "obligatory looking" (difficulty disengaging visual attention) around 1 month. Finally, that maturation of the cortical layer 4 at 2 months and subsequently layers 2 and 3 at 3 months allows for development of anticipatory eye-movements, which may correspond with the development of covert attention (Rothbart, Posner, & Boylan, 1990).

Exogenous orienting. An investigation overt orienting in an exogenous cuing paradigm demonstrated limited orienting and no facilitation or inhibition in 2-month-olds, but clear orienting to targets including facilitation and inhibition due to peripheral cues by 4 months of age (M. H. Johnson & Tucker, 1996). Additionally, the speed at which infants shift their spatial attention increases from 4 to 7 months. Similarly, the development of covert attention appears to be present by 4 months of age (M. H. Johnson, Posner, & Rothbart, 1994). Furthermore, 4-month-old infants more easily disengage visual attention compared to 2- and 3-month-olds (Frick, Colombo, & Saxon, 1999; M. H. Johnson, Posner, & Rothbart, 1991). In 2-, 4-, and 6-month-old infants, efficiency of disengagement increased with age (McConnell & Bryson, 2005). These results suggest visual-spatial orienting functions develop rapidly during the first year of life.

Prior research in school-age children and adolescents has demonstrated that orienting functions and their neurocognitive networks continue to develop into adolescence.

Wainwright and Bryson (2002) examined orienting to exogenous predictive cues in children aged 6, 10, and 14 years and adults during a target detection task. Six-year-old children showed increased costs associated with invalid cues compared to other age groups, suggesting that younger children may be more inefficient at disengaging attention. Schul et al. (2003) examined target discrimination to exogenous predictive cues and demonstrated clear age-related changes in orienting efficiency. Results indicate that the ability to efficiently orient attention to exogenous cues increases between 7 and 18 years of age and that the validity effect for volitional, but not reflexive, orienting continues to develop during school-age and adolescent years. These findings are in agreement with a study of 8- and 11-year-old children and adults by Pearson and Lane (1990), which demonstrated that the speed of attentional shifting continues to increase with age.

The development of orienting abilities has also been examined using the ANT (previously described). Findings suggest that orienting efficiency increases between the ages of 4 and 7 years (Mezzacappa, 2004). However, no change in orienting score was exhibited from 6 years of age through adulthood (Rueda et al., 2004). This finding may be task-dependent as the paradigms did not include invalid trials, thus reducing the amount of attentional disengagement necessary to complete the task. Neuroimaging findings, using a modified ANT (which included invalid trials), demonstrated that children (8 to 12 years) exhibited reduced activity in the right temporal-parietal junction during attentional reorienting and exhibited increased activation relative to adults in superior frontal gyrus and insula, suggesting that the regions associated with attentional reorienting and voluntary control of attention have yet to reach adult-like levels of function (Konrad et al., 2005).

Endogenous orienting. By the age of 3 months, infants are sensitive to direction of gaze and direct their attention towards gaze-cued locations; however, if the endogenous gaze-cue remains onscreen (as opposed to being removed prior to the appearance of the target) 3-

month-olds did not orient attention to the gaze-cued location as frequently, perhaps due to difficulties disengaging visual attention (Hood, Willen, & Driver, 1998).

Ristic and colleagues (2002) demonstrated reflexive orienting to both non-predictive, endogenous gaze and arrow cues in 3- to 5-year-old children, although the degree of the validity effect was significantly different compared to adults. Wainwright and Bryson (2005) examined orienting to an endogenous arrow cue in children aged 6, 10, and 14 years and adults for a target detection task. Between groups analysis revealed similar validity effects across groups; however, within group analysis revealed that unlike the rest of the age groups, 6-year-old children did not demonstrate an increased validity effect, suggesting that volitional control of attention may still be developing. In accord with this finding, cross sectional research using endogenous cuing paradigms suggests that the development of orienting reaches adult-like levels by 8 to 9 years of age (Goldberg, Maurer, & Lewis, 2001).

Visual Search. In addition to paradigms associated with visuo-spatial orienting, visual search paradigms have also been used to investigate selective attention associated with the orienting network. However, these two tasks (visuo-spatial cuing vs. search) may tap unique neural systems (Luck, Hillyard, Mangun, & Gazzaniga, 1989). Visual search paradigms require participants to identify the presence or absence of a predefined target that is located within an array of distractor items. Search difficulty is dependent on factors such as the number of items within the array (set size) and the similarity of target and distractors. Search efficiency is measured by the slope of the RT by set size function (ms/item). Although prior research on the development of visual search abilities has demonstrated no age-related changes in search efficiency (slope) for simple feature and conjunctive searches (Hommel, Li, & Li, 2004; Lobaugh, Cole, & Rovet, 1998), children show steeper slopes (i.e., are less efficient searchers) on more difficult conjunction searches compared to adults (Donnelly et al., 2007; Merrill & Lookadoo, 2004; Trick & Enns, 1998). Search performance relative to a

simple RT task appears to be disproportionally affected by the presence of distractors in younger age groups, suggesting that children may be distracted to a greater degree by the mere presence of distractors (Hommel et al., 2004).

In summary, similar to the alerting network, the development of the subcomponents of visuospatial orienting – shifting and disengaging - seem to be established by the middle of the first year of life. Behaviorally, the efficiency of exogenous and endogenous orienting mechanisms continue to develop into the school-age period, reaching adult-like levels around 10 to 12 years of age. However, differences in neuroimaging findings suggest that specialization of the regions may continue into adolescence. Results from visual search suggest that efficiency of selective attention mediated, in part, by the orienting network continues to develop into adolescence, and may reflect increased abilities to filter irrelevant information.

Orienting function in ASD. Deficits in orienting visual attention have been consistently observed in individuals with ASD. Evidence in support of early orienting deficits has been supplied by observational studies and retrospective video analysis of infants and toddlers diagnosed with ASD, and, more recently, from prospective studies of infants at-risk for ASD. Using retrospective home video analysis, Baranek (1999) compared ASD, TD, and DD infants between 9 and 12 months of age. She reported that ASD infants oriented to visual stimuli less than TD and DD infants, 65% to 81% and 85%, respectively. Maestro et al. (2002) demonstrated that, within the first 6 months of life, infants with ASD do not orient towards people or human voices as frequently as TD infants. Additionally, infants with ASD have been shown to orient to name significantly less as compared to TD and DD infants (Osterling & Dawson, 1994; Osterling et al., 2002).

Observational studies have revealed similar orienting deficits in ASD. Swettenham and colleagues (1998) measured spontaneous shifts of attention while 20-month-old ASD, TD,

and DD infants participated in a five-minute free play session, and demonstrated that, in general, infants with ASD showed less attention shifting compared to the two comparison groups. Dawson and colleagues (1998) examined orienting to a variety of social and nonsocial stimuli in 5-year-old children with ASD, Down syndrome, and MA-matched TD toddlers. Results indicated that children in the ASD group failed to orient to both social and nonsocial stimuli as frequently as the comparison groups, and, furthermore, those children with ASD who were able to orient attention demonstrated delayed orienting to social stimuli. In a larger follow-up study, Dawson and colleagues (2004) replicated previous findings and showed that children with ASD failed to orient as frequently to social and nonsocial stimuli compared to the comparison groups.

Exogenous orienting. In older children, adolescents, and adults with ASD, orienting abilities have been measured using various Posner cuing paradigms. Prior studies examining exogenous orienting in ASD have demonstrated slower shifting of attention compared to TD individuals (Townsend, Harris, & Courchesne, 1996). In a comparison of TD, ASD, and cerebellar lesion participants, Townsend et al. (1999) replicated previous findings (Townsend et al., 1996), and furthermore demonstrated that shifting efficiency was related to area of cerebellar vermis VI-VII, such that slower orienting was related to decreased vermis area. A similar study that included children with ASD reported no difference in RT validity effect; however, similar to adults, children with ASD evidenced a significant correlation between the shifting efficiency and cerebellar vermis area (Harris, Courchesne, Townsend, Carper, & Lord, 1999).

More recently, Renner and colleagues (2006) demonstrated intact endogenous, but impaired exogenous, orienting in children and adolescents with ASD. Furthermore, for the ASD group, motor impairment (an indirect measure cerebellar function) was inversely related to validity effect for the exogenous task. The authors suggest that this finding may support

previous findings of a relationship between orienting abilities and cerebellar volumes (Harris et al., 1999; Townsend et al., 1999).

An fMRI investigation of exogenous orienting (Haist, Adamo, Westerfield, Courchesne, & Townsend, 2005) demonstrated that individuals with ASD showed reduced activation in left and right inferior parietal lobe at the short SOA relative to TD individuals. The long SOA was associated with more extensive activation in the ASD group (relative to the short SOA) and a greater degree of overlapping activation in both ASD and TD individuals. The authors suggest that these findings are indicative of an impaired network underlying reflexive orienting and relatively spared, though still atypical, network underlying more voluntary orienting in ASD.

Endogenous orienting. Surprisingly, prior research using endogenous cuing paradigms have generally failed to find differences in orienting abilities in ASD. Using a non-predictive endogenous cue (gaze), Sweetenham and colleagues (2003) demonstrated equivalent orienting between ASD and TD children to both upright and inverted faces. Subsequent use of similar endogenous arrow and gaze cuing paradigms have also reported equivalent orienting in children with ASD (Chawarska, Klin, & Volkmar, 2003; Greene et al., in press; Kylliainen & Hietanen, 2004; Senju, Tojo, Dairoku, & Hasegawa, 2004), although some evidence suggests that gaze cues may be processed differently in ASD (Chawarska et al., 2003; Greene et al., in press; Vlamings, Stauder, van Son, & Mottron, 2005).

Ristic et al. (2005) examined predictive and non-predictive orienting to endogenous gaze cues in two groups of adolescents with ASD. Individuals with ASD evidenced similar validity effects for predictive, but not for non-predictive, cues compared to TD individuals. According to the authors, these findings suggest that individuals with ASD do not reflexively orient attention to shifts in gaze but can use volitional control of attention. In agreement with the results of Ristic et al. (2005), Goldberg and colleagues (2008) reported that children with

ASD do not demonstrate a validity effect to non-predictive endogenous gaze cues similar to TD children.

Disengagement of attention. Prior research investigating disengagement of attention in ASD has revealed impairments in at-risk infants (Elsabbagh et al., 2009; Zwaigenbaum et al., 2005) and school-age children (Landry & Bryson, 2004) and adults (Kawakubo et al., 2007) with ASD. Specifically, Landry and Bryson (2004) demonstrated that children with ASD showed significantly increased latencies to disengage visual attention compared to CA-matched children with Downs syndrome and MA-matched TD children. Additionally, the authors report that the frequency of fast attentional shifts (within 100-300ms) was significantly reduced in the ASD group, suggesting that in addition to difficulty disengaging attention, children with ASD did not efficiently shift attention to the target (similar to findings discussed above).

Attentional disengagement has also been examined in at-risk infants. Zwaigenbaum and colleagues (2005) investigated attentional disengagement in high-risk infants at 6 and 12 months. At 6 months there was no difference between high- and low-risk infants in their ability to shift or disengage visual attention. Importantly, when retested at 12 months, the high-risk group evidenced poorer performance in disengaging visual attention. Specifically, 25% of high-risk infants demonstrated *longer* latencies to disengage attention. Interestingly, all of the children that exhibited increased difficulties disengaging attention between 6 and 12 months received an ASD diagnosis at 24 months. Analogously, the ability to disengage visual attention at 12 months was predictive of ASD symptomatology at 24 months. In addition, Elsabbagh and colleagues (2009) have also demonstrated that infant siblings of children with ASD (9-10 months) evidence increased difficulty disengaging attention.

Kawakubo and colleagues (2007) examined the electrophysiology of attentional disengagement in low-functioning adults with ASD. Behaviorally, adults with ASD

evidenced increased latencies to disengage attention compared to TD and DD individuals. Electrophysiological results demonstrate increased pre-saccadic positivity but equivalent pre-saccadic spike in ASD as compared to TD and DD individuals. The authors hypothesize that greater pre-saccadic positivity suggests that the ASD group may require more resources in order to disengage visual attention. It should be noted that evidence of intact attentional disengagement in ASD has also been observed (Goldberg et al., 2002; Kawakubo, Maekawa, Itoh, Hashimoto, & Iwanami, 2004; Leekam, Lopez, & Moore, 2000; Mosconi et al., 2009), though individuals with ASD in one of these studies (Goldberg et al., 2002) did make fewer express saccades (short latency saccades occurring between 80 – 140 ms) to the target.

Because overt orienting involves eye-movements, oculomotor control in ASD will be briefly discussed (see Brenner, Turner, & Muller, 2007, for review). Previously, Takarae et al. (2007) reported that during reflexive visually-guided saccades, adults with ASD exhibited increased activation of dorsolateral prefrontal cortex, anterior cingulate, and caudate nucleus relative to TD adults, suggesting that they may rely on areas responsible for voluntary control of attention in order to perform more reflexive shifts of attention. Individuals with ASD also exhibit hypometric saccades (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007; Takarae, Minshew, Luna, & Sweeney, 2004), as well as other oculomotor abnormalities characteristic of cerebellar dysfunction (Nowinski, Minshew, Luna, Takarae, & Sweeney, 2005). Individuals with ASD further demonstrate abnormally increased saccade frequency, which may indicate that the neural system underlying saccade generation may be dysfunctional in ASD (Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1998).

Visual Search. Despite deficits in orienting and disengaging attention, individuals with ASD excel at visual search (see Dakin & Frith, 2005, for review). Prior research has shown that children (O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001), adolescents (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009), and adults (O'Riordan, 2004) with ASD

demonstrate faster RT compared to their TD peers for a variety of visual search tasks. O'Riordan and colleagues (2001) found that children with ASD demonstrate shallower RT by set size slopes compared to the TD children, indicating the cost of additional distractors was greater in TD as compared to ASD participants. Subsequent research by O'Riordan (2000) showed that faster search times for individuals with ASD was not the result of greater top-down modulation of attention. Rather, evidence from O'Riordan and Plaisted (2001) suggests that search advantage in ASD is related to enhanced visual discrimination. This was confirmed by Joseph and colleagues (2009), who reported reduced RT by set size y-intercepts and reduced fixation durations in ASD, both indicative of faster perceptual encoding at the locus of attention.

In ASD, orienting deficits appear to be present within the first year of life. Retrospective analysis of home videos and prospective analysis of at-risk infant siblings have demonstrated that before their first birthday, infants later diagnosed with ASD exhibit impairments in disengaging and shifting their attention to both social *and* nonsocial stimuli within their environment. Furthermore, investigations of children, adolescents, and adults with ASD have revealed that these individuals show slower, less efficient orienting abilities. Although results are conflicting, evidence suggests that reflexive orienting may be more impaired compared to volitional shifts of attention. Townsend and Courchesne (1994) demonstrated that adults with ASD and parietal lobe abnormalities demonstrate enhanced sensory processing within a *narrower* attentional spotlight. The authors suggest that this less distributed spotlight may restrict processing peripheral cues resulting in poorer responsivity to information outside this area. Interestingly, this narrower, more over-focused attention may also result in enhanced discrimination at the focus of attention and superior visual search abilities in ASD.

Executive Control Network

The executive control network is a multidimensional attentional system, responsible for inhibition, planning, error monitoring, set shifting, working memory, and cognitive flexibility. Recent studies have shown that executive control is not mediated by a unitary mechanism, but can be dissociated into *at least* three separate but associated functions (set shifting, working memory, and inhibition) in TD children and adults (Huizinga, Dolan, & van der Molen, 2006; Miyake et al., 2000; see Smith & Jonides, 1999, for different taxonomy of executive mechanisms). Set shifting refers not to visuospatial orienting (previously reviewed), but rather to shifting between multiple mental sets (also referred to as "task switching;" Monsell, 2003). Working memory function corresponds to active monitoring, updating, and maintenance of task-relevant information. Finally, inhibition refers to an individual's ability to inhibit prepotent or automatic responses. These three domains of executive functions will be the focus of the following section.

Importantly, although executive control can (and should) be divided into separate components, the interaction between components is essential for successful performance of many executive control tasks (Miyake et al., 2000; Roberts & Pennington, 1996). For example, in the anti-saccade task (designed to test inhibitory processes), participants attend to a central fixation and make saccades to the mirror (opposite) location at the onset of peripheral flashes. Participants must maintain instructions in working memory while inhibiting prepotent responses (i.e. making saccade towards peripheral flash). Two important considerations should be kept in mind when comparing different populations on executive tasks. First, while designed to test inhibitory function, subtle lapses in working memory may ultimately result in poorer performance (i.e., apparent inhibitory deficits in clinical populations may result from dysfunctional working memory processes and not abnormal inhibitory control). Second, the degree of prepotencies may differ between groups such that the cost of inhibiting saccades to

peripheral flashes is weaker in one group, resulting in the erroneous appearance of superior inhibition.

Omnibus tests such as the Wisconsin Card Sorting Task (WCST) and the Tower of Hanoi (ToH) or the similar Tower of London (ToL) have been employed extensively to test executive control in ASD. However, because these tasks simultaneously tap multiple executive functions, their explanatory significance is limited. Therefore, only tasks that attempt to isolate (at least to some degree) set shifting, working memory, or inhibitory executive control functions will be discussed.

The neural substrates of executive control include regions within the prefrontal cortex – the orbitofrontal cortex (OFC), the ventrolateral prefrontal cortex (VLPFC), and the dorsolateral prefrontal cortex (DLPFC) – as well as medial frontal regions (anterior cingulate cortex; ACC) and subcortical regions such as the basal ganglia and cerebellum (Heyder, Suchan, & Daum, 2004). Additionally, more posterior areas (mainly located in the parietal lobe) may also be important for the performance of executive processes (Collette et al., 2005; Wager, Jonides, & Reading, 2004; Wager & Smith, 2003). More specifically, the right inferior frontal cortex may mediate inhibitory processes (Aron, Robbins, & Poldrack, 2004) while bilateral dorsal frontal regions (superior frontal sulcus, DLPFC) are important for updating working memory and right ventral frontal regions are important for manipulating information in working memory (Wager & Smith, 2003). Set shifting may be mediated by bilateral medial frontal cortex (ACC), intraparietal sulci, and to a lesser degree anterior insula and DLPFC (Wager et al., 2004). Finally, the ACC is associated with inhibiting prepotent responses, response monitoring, and error detection (Botvinick, Cohen, & Carter, 2004).

Executive control function in typical development. Relative to the attention networks discussed above, the executive control network undergoes the most protracted

development (see Diamond, 2002, for review), with each executive component sustaining a separate developmental time course.

Set Shifting. Few studies have examined the development of set shifting abilities; however, the current literature suggests that this executive component continues to develop through 8 to 13 years of age (Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003), and does not reach adult levels until approximately 15 years of age (Huizinga et al., 2006). Surprisingly, performance on a measure of set shifting, the Intradimensional/Extradimensional (ID/ED) subtest of the CANTAB, appears to reach adult levels by approximately 8 years of age (De Luca et al., 2003; Luciana & Nelson, 1998). However, this early maturation may be task-dependent. Switching tasks with larger inhibitory and/or working memory demands may result in a slower, more prolonged developmental trajectory.

Working memory. The ability to hold information in working memory is present in the first year of life. Working memory functions (e.g., capacity and the ability to manipulate online information) develops gradually during the preschool period (see Garon, Bryson, & Smith, 2008, for review). In contrast to inhibitory processes (discussed below), working memory continues to develop between 8 and 13 years of age (Lehto et al., 2003) and into adolescence, reaching adult-like levels after age 15 (Huizinga et al., 2006). The verbal and non-verbal components of working memory appear to follow similar linear increases in performance between 4 and 15 years of age (Gathercole, Pickering, Ambridge, & Wearing, 2004).

Results from cross-sectional studies of performance on the Spatial Working Memory CANTAB subtest are consistent with this developmental trajectory. Specifically, adult-like performance is achieved around the age of 15 years old (De Luca et al., 2003; Luciana, Conklin, Hooper, & Yarger, 2005). Furthermore, results from cross-sectional studies of

memory-guided saccade performance have revealed that the latency and accuracy of the initial saccade mature by approximately 14-15 years of age (Luna, Velanova, & Geier, 2008).

Inhibition. Simple inhibitory processes come online within the first year of life and develop during preschool years, while more complex inhibitory processes (those that include a larger working memory component) appear later in preschool and continue to develop through the school-age years (Garon et al., 2008). Inhibitory processes are the first to reach adult-like levels (Lehto et al., 2003); however, inhibition itself may not be a unitary concept (Friedman & Miyake, 2004), and thus the development of discrete inhibitory processes may mature at different rates (Huizinga et al., 2006). By 11 years old, children perform at adult levels on the Eriksen Flanker task and Stop-Signal task (Huizinga et al., 2006). The executive control score provided by the ANT (similar to the Eriksen Flanker task), decreases between 4 and 7 years (Mezzacappa, 2004; Rueda et al., 2004), and remains static from the age of 7 into adulthood (Rueda et al., 2004). Similarly, there appears to be no relationship between age and inhibition between the ages of 8 and 13 years (Lehto et al., 2003). However, performance on the anti-saccade task does not reach adult levels until 14 to 15 years of age (Luna et al., 2008).

In summary, executive control is not a unitary construct, but instead consists of at least three independent, but associated components: set shifting, working memory, and inhibition. These components are mediated primarily by prefrontal cortex and undergo more protracted development compared to the previous attentional networks. Moreover, each executive component follows a distinct developmental trajectory, reaching adults levels at varying times between early and late adolescence.

Executive control function in ASD. Of the three attentional functions (alerting, orienting, and executive control) discussed thus far, executive control is by far the most studied attention component in ASD (see Geurts, Corbett, & Solomon, 2009; Hill, 2004a, 2004b; O'Hearn, Asato, Ordaz, & Luna, 2008; Ozonoff, South, & Provencal, 2005; Russo et

al., 2007, for reviews). In their review, Ozonoff and colleagues (2005) concluded that individuals with ASD demonstrate relatively intact inhibitory and working memory processes, but impaired cognitive flexibility/set shifting abilities (see Geurts, Corbett, et al., 2009, for discussion of intact cognitive flexibility). Although previously thought to be a primary deficit in ASD, the absence of early executive control deficits in 3- to 4-year-old children with ASD (Dawson et al., 2002; Griffith, Pennington, Wehner, & Rogers, 1999; Yerys, Hepburn, Pennington, & Rogers, 2007) suggest that executive control deficits may be secondary to the development of ASD. However, impairments in executive control in ASD are present by 5 years of age (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; McEvoy, Rogers, & Pennington, 1993).

Before discussing specific executive deficits in ASD, it is necessary to briefly discuss two caveats: 1) the relationship between executive control and IQ, and 2) the comorbidity of ASD and ADHD. First, the relationship between IQ and executive abilities in individuals with ASD (Liss et al., 2001; Lopez, Lincoln, Ozonoff, & Lai, 2005; Steele, Minshew, Luna, & Sweeney, 2007; Williams, Goldstein, Carpenter, & Minshew, 2005) suggests that inclusion of lower-functioning individuals may likely result in between-group differences in executive control abilities. As such, matching ASD and TD groups based on verbal versus non-verbal IQ may result in different outcomes (impaired when matched by NVIQ; intact when matched by VIQ) (Russo et al., 2007). Therefore, between group differences and within group variability of general cognitive abilities must be accounted for when investigating executive functions in ASD.

Second, recent estimates of children and adolescents with ASD suggest that approximately 30% meet criteria for a comorbid diagnosis of ADHD (Leyfer et al., 2006; Simonoff et al., 2008). Furthermore, individuals with ASD with and without a diagnosis of ADHD have demonstrated different profiles of executive impairment (Sinzig, Morsch,

Bruning, Schmidt, & Lehmkuhl, 2008; Yerys et al., 2009). Thus, the inclusion or exclusion of children and adults with ASD and ADHD may contribute to the conflicting findings within the executive control literature.

Set shifting. Initial evidence of impaired set shifting in ASD was established with the robust and well-replicated finding of perseverative deficits on the WCST (see Hill, 2004a; Ozonoff et al., 2005, for review of findings); however, as discussed above, the WCST is not a pure measure of set shifting abilities, and thus impaired performance in ASD may be due to a number of alternative factors (see Geurts, Corbett et al., 2009, for a more detailed discussion).

Investigators have begun to use the CANTAB ID/ED subtest as a measure of shifting in ASD, though results from these studies are conflicting. Earlier studies reported impaired set shifting abilities in ASD as compared to non-autistic comparison groups (Hughes, Russell, & Robbins, 1994; Ozonoff et al., 2004). However, more recent investigations have failed to find shifting impairments in children and adolescents with ASD (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Goldberg et al., 2005; Happe, Booth, Charlton, & Hughes, 2006). The absence of shifting impairments is surprising given the prior findings of impaired shifting on the WCST; however, equivalent ASD and TD performance may result from reduced sensitivity of the task (as discussed above, TD children reach adult-like levels of performance around the age of 8) due to ceiling effects (Goldberg et al., 2005). Nevertheless, the absence of set shifting deficits in ASD suggests that children and adolescents with ASD are capable of shifting mental sets.

Shifting attention has also been examined with a cross-modal shifting paradigm. Courchesne and colleagues (1994) demonstrated that adults with ASD show difficulties shifting attention between modalities similar to individuals with cerebellar lesions. However, these deficits reflect slowed rather than absent shifts as both groups were able to shift attention when given more time (>2.5s). Electrophysiological results from the same paradigm suggest

poor performance by individuals with ASD may result from aberrant distribution of attentional resources (as indexed by the slow negative wave; SNW) (Ciesielski, Knight, Prince, Harris, & Handmaker, 1995).

Shafritz et al. (2008) examined neural substrates of set shifting and inhibitory processes in adults with ASD in a modified odd-ball paradigm using fMRI. Participants were required to give one response to standards (94%; squares) and distractor-rares (3%) and a different response to target-rares (3%). The identity of the target (either triangles or circles) was switched every two blocks. Thus, the task consists of an inhibition component (inhibiting prepotent distractor response for target-rares) and a set-shifting component (switching target-rare identity). Behaviorally, individuals with ASD did not evidence increased switching cost (i.e., greater errors on switching run versus maintain runs); however, individuals with ASD did exhibit increased error rates for target-rares regardless of switching condition. Activation analyses revealed decreased activation in DLPFC, basal ganglia, and intraparietal sulcus in ASD compared to TD for target trials, but no differential effect for maintain versus switching blocks. Behavioral and activation results indicate impaired performance and atypical neural response to inhibition, but not set switching, components of the task in ASD.

The results of the studies reviewed above suggest that shifting deficits may be less pervasive than previously thought. This is in agreement with a recent review of the ASD cognitive flexibility literature by Geurts and colleagues (2009), which suggests that set shifting may not be dysfunctional in ASD.

Working memory. The results of studies examining working memory in ASD are inconsistent, possibly due to the varying degree of capacity, maintenance, and manipulation demands of each task. Prior studies using the A-not-B task to examine young children with ASD have demonstrated intact working memory in 3 year-old children with ASD compared to MA-matched TD and DD children (Dawson, Munson et al., 2002; Griffith et al., 1999; Yerys

et al., 2007). However, by the age of 5, children with ASD perform poorer as compared to TD children on tasks requiring working memory processes (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; McEvoy et al., 1993).

Bennetto and colleagues (1996) report impairments on verbal working memory tasks for adolescents with ASD compared to TD individuals. However, poorer performance on these paradigms may be due to the use of a dual-task. Individuals were required to hold to-be-recalled information while continuing to fill in the final words to sentences or counting dots. Garcia-Villamisar and Della Sala (2002) demonstrated equivalent performance in a single-task working memory condition, but impaired performance in dual-task working memory condition in adults with ASD, suggesting that the ASD impairments demonstrated by Bennetto et al. (1996) may be due to the dual-task component of the working memory paradigm.

In contrast, Russel and colleagues (1996) and Ozonoff and Strayer (2001) found no impairments on a variety of working memory tasks in children with ASD relative to non-autistic comparison groups. Adults with ASD have also been shown to have equivalent RT and accuracy performance on 0- 1- and 2-back tasks compared to TD adults (Koshino et al., 2005). Williams and colleagues (2005) reported equivalent performance of verbal working memory (N-back, Letter-Number Sequencing), but impaired spatial working memory performance (Spatial Span, Finger-Windows subtests) in children and adults with ASD. More recently, impaired spatial working memory performance in children and adults with ASD has also been reported using the CANTAB Spatial Working Memory subtest (Corbett et al., 2009; Goldberg et al., 2005; Happe et al., 2006; Steele et al., 2007).

Studies employing memory-guided saccade tasks have reported deficits in saccade accuracy in children and adults with ASD (Luna et al., 2007; Minshew, Luna, & Sweeney, 1999) and slower saccade latency but similar accuracy (Goldberg et al., 2002) compared to

TD individuals. Additionally, adults with ASD evidenced reduced activation of DLPFC during a memory-guided saccade task compared to TD adults (Luna et al., 2002). However, as discussed above, abnormal performance on eye-movement measures may be due to abnormal oculomotor function in ASD.

Koshino and colleagues (2005) examined activation and connectivity of brain regions involved in an N-back task in adults with ASD. The authors observed similar behavioral performance, but different patterns of activation and reduced functional connectivity between regions in ASD compared to TD individuals. Specifically, adults with ASD relied on right frontal-parietal regions to a greater extent compared to TD adults who evidenced bilateral frontal-parietal activation, perhaps resulting from unique strategies employed by each group. Additionally, the number of regions associated with the working memory network was reduced in ASD and the functional connectivity between regions was generally weaker.

At first glance, the results of the working memory studies reviewed appear inconsistent. Yet, close inspection suggests that the working memory deficits may be due to cognitive load (Garcia-Villamisar & Della Sala, 2002) and/or poor or inefficient use of strategies (Corbett et al., 2009; Steele et al., 2007). Neuroimaging evidence is in accord with these hypotheses, indicating that inefficient functional connectivity between regions may, in part, play a role in poorer ASD performance during more complex or dual-task conditions. In addition, atypical activity during working memory performance suggests that individuals with ASD may rely on less efficient strategies, which may result in impaired performance during more difficult working memory tasks (Koshino et al., 2005).

Inhibition. As discussed above, inhibitory processes seem to function similarly in young children with ASD and in TD children (Dawson, Munson et al., 2002; Griffith et al., 1999; Yerys et al., 2007); though executive impairments begin to manifest themselves by the age of 5 (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; McEvoy et al., 1993).

Correspondingly, prior research has revealed an absence of developmental improvement in inhibitory abilities for individuals with ASD (Luna et al., 2007; Ozonoff, Strayer, McMahon, & Filloux, 1994; Solomon, Ozonoff, Cummings, & Carter, 2008).

For individuals with ASD, tasks that tend to isolate inhibitory processing from other executive functions (e.g Ozonoff & Strayer, 1997) have regularly showed equivalent performance to TD individuals; however, when measures of inhibition are paired with other executive components (e.g. set switching), deficits in inhibitory abilities may be observed in ASD (Ozonoff et al., 1994). This is in accord with the theory put forth by Minshew and colleagues (1997), which posits that individuals with ASD tend to have more difficulty with tasks that require more cognitive resources (e.g., Rinehart, Bradshaw, Tonge, Brereton, & Bellgrove, 2002).

The majority of previous studies have demonstrated *intact* inhibitory abilities in ASD for Go-NoGo (Geurts, Begeer, & Stockmann, 2009; Happe et al., 2006; Kana, Keller, Minshew, & Just, 2007; Ozonoff & McEvoy, 1994; Raymaekers, Antrop, van der Meere, Wiersema, & Roeyers, 2007; Raymaekers, van der Meere, & Roeyers, 2004; Raymaekers et al., 2006), Eriksen flanker (Henderson et al., 2006), Start-Signal (Ozonoff & Strayer, 1997), Negative Priming (J. A. Brian, Tipper, Weaver, & Bryson, 2003; Ozonoff & Strayer, 1997), and Stroop (Adams & Jarrold, 2009; Ambery, Russell, Perry, Morris, & Murphy, 2006; Bryson, 1983; Christ, Holt, White, & Green, 2007; Eskes, Bryson, & McCormick, 1990; Goldberg et al., 2005; Ozonoff & Jensen, 1999; Russell, Jarrold, & Hood, 1999) paradigms. However, results from anti-saccade tasks have consistently demonstrated inhibitory impairment in children and adults with ASD (Goldberg et al., 2002; Luna et al., 2007; Minshew et al., 1999; Mosconi et al., 2009; Thakkar et al., 2008). As discussed above, performance on the anti-saccade task reaches adult-like levels at a much later age as compared to other inhibitory tasks. This indicates that the prepotency to make a saccade towards a

peripheral target may be one of the more difficult actions to inhibit, and therefore requires an extended period in order to mature.

Neuroimaging results suggest that despite the equivalent behavioral performance between ASD and TD individuals, adults with ASD evidence reduced activation in the inferior frontal gyrus and ACC as well as reduced functional connectivity between the "inhibition network" (bilateral cingulate gyri and insulae) and inferior frontal and parietal gyri during a Go-NoGo task (Kana et al., 2007). The authors suggest that the network responsible for inhibitory processes may not function in a well-coordinated fashion with other regions necessary for successful inhibitory performance in individuals with ASD. A more recent fMRI study using a similar task revealed that functional connectivity between these regions may decrease with age in children and adolescents with ASD (Lee et al., 2009).

In summary, although previously thought to be a primary deficit in ASD, the absence of early executive control deficits in preschool-aged children with ASD (Dawson, Munson et al., 2002; Griffith et al., 1999; Yerys et al., 2007) suggests that executive control deficits may be secondary to the development of ASD. The degree to which executive control abilities improve with development remains unclear. The trajectory of development appears similar in ASD and TD individuals (Luna et al., 2007); however, there are conflicting reports of age-related improvement (Happe et al., 2006) or decline (Lee et al., 2009; Solomon et al., 2008), which may be related to the executive component tested (Ozonoff et al., 2004).

The Role of Attention in the Development of Sociocommunicative Function

Research examining the role of attention in the development of social and communicative functions has revealed that domain-general attention functions may play an important role in the development of these abilities. The majority of this evidence comes from research on infant temperament. Temperament has been defined as "constitutionally based individual differences in emotional, motor, and attentional reactivity and self-regulation"

(Rothbart & Bates, 1998, p. 109). Rothbart and Bates (1998) have discussed the link between constructs of temperament research and the alerting, orienting, and executive control networks. In general, reactivity (e.g., response to novelty) can be associated with alerting and orienting networks, whereas self-regulation and effortful control can be related to executive mechanisms.

Two studies have examined the relationship between early attentional function and measures of temperament. McConnell and Bryson (2005) showed that 4-month-old infants that had greater difficulty disengaging their attention were rated as more fearful of novel stimuli. Similarly, Johnson and colleagues (1991) found increased aversion to novelty was related to slower to disengage attention in 4-month-old infants. Previous research has demonstrated that orienting attention towards a distraction temporally suspends distress in infants (Harman, Rothbart, & Posner, 1997). For instance, during face-to-face interactions, infants shift attention away from faces in order to regulate arousal levels (Field, 1981). Disengaging and shifting attention are important early mechanisms for regulating arousal, and, thus slowed or impaired disengagement may result in greater negative reactivity to novel information.

Sanson (2004) has recently reviewed the association between temperament and social development. She concludes that both high self-regulation and low negative reactivity are related to the development of increased social skills. Conversely, high reactive infants (i.e., those that respond negatively to novel situations) are more likely to have poorer peer relations. In addition, early effortful control measures have also been shown to be related to social functioning and regulating affect and may play an important role in socioemotional development (Kochanska, Murray, & Harlan, 2000).

Joint attention, which refers to the ability of a child to coordinate his/her attention with a social partner, has important implications for the development sociocommunicative

skills. Although joint attention abilities develop rapidly, they are based on more basic orienting mechanisms (see Frischen, Bayliss, & Tipper, 2007, for review). Because parents name objects at the locus of child's attention, the attentional response of the child has important consequences as it prompts parents to label objects within the child's environment (Lempert & Kinsbourne, 1985). Similarly, infant shifts of attention corresponding to the locus of caregiver's attention (along with subsequent naming) may facilitate vocabulary growth (Baldwin, 1995). Previous research indicates that earlier joint attention abilities have been shown to predict both vocabulary size (Morales et al., 2000) and theory of mind abilities (Charman et al., 2001). Therefore, impairments in orienting functions such as disengaging or shifting attention would likely have important consequences for the development of joint attention abilities and associated high-level abilities.

As reviewed above, the development of higher-level sociocommunicative abilities is dependent on intact function of lower-level attentional mechanisms. However, further investigations are necessary to link specific early attentional abilities during typical development to more detailed measures of social and communicative functions later in life. In addition, understanding the early attentional deficits in ASD and their role in the development of sociocommunicative impairments will also help elucidate the role of attentional mechanisms in the development of high-level functions.

Evidence Relating ASD to Impairments in Attention

Theories of autism have postulated primary impairments in both social and nonsocial functions (see Happe, 2001, for more in-depth discussion). While the focus of this section is the role of attention in the development of ASD, this is not meant to imply that impaired attentional modulation is the only primary disturbance in ASD. As was aptly put by Goodman, "the very diversity of existing 'unitary' psychological and neurological explanations casts doubt on the hypothesis that infantile autism can potentially be explained

by a fault in just one psychological or neurological system" (Goodman, 1989, p. 410). Rather, the goals of understanding whether dysfunctional attentional processes are of etiological significance in ASD is two-fold. If early attentional impairments play a causal role in the development of ASD then 1) attentional deficits may be used as an early behavioral marker that can be used to identify infants at-risk for ASD and 2) the development of attention-targeted early interventions that may remediate abnormal developmental trajectories and improve outcome in children with ASD.

Previous researchers have hypothesized that alerting (Dawson & Lewy, 1989; Gold & Gold, 1975), orienting (Courchesne, Townsend, Akshoomoff, Yeung-Courchesne et al., 1994; Ornitz, 1988), and executive deficits (Ozonoff, Pennington, & Rogers, 1991) may contribute to the development of ASD. As reviewed above, individuals with ASD demonstrate abnormal function of all three attentional networks; evidence relating atypical attention function to sociocommunicative impairments in ASD will be discussed below.

Alerting Network. Gold and Gold (1975) and Dawson and Lewy (1989) have both hypothesized that aberrant function of the alerting/arousal system may lead to the development of sociocommunicative ASD impairments. The dynamic features and complexity of social stimuli and unpredictable nature of social interaction may be overarousing to individuals with ASD. This hyperarousal would result in inattention and dysfunctional processing of social information.

Evidence in support of the link between attention and social information processing comes from Pierce and colleagues (1997) who examined social perception skills in ASD. Multiple videotaped vignettes of social interactions in which the number of social cues was varied were used. The authors reasoned that, if ASD deficits in social abilities are due to impaired perception of social information, then trials with redundant social information (i.e. multiple cues) should improve task performance; however, if ASD social deficits are related to

an attentional impairment, then task performance should improve in conditions with reduced attentional requirements (i.e. single cue condition). Children with ASD performed similar to CA-matched DD children and VMA-matched TD children on the interpretation of social situations with single social cues, but significantly worse on trials in which multiple social cues were available. These findings suggest that impaired perception of social stimuli may be the result of abnormal general information processing deficits, perhaps due to overarousal, and not to social information processing deficits specifically.

Gold and Gold (1975) and Dawson and Lewy (1989) also hypothesized that because of an inherently unstable arousal system, novel stimuli may be perceived as aversive in infants and children with ASD, thus resulting in abnormal perception of novelty. As previously discussed, children with ASD demonstrate abnormal behavioral and neural indices (e.g., reduced P3 amplitude) of novelty processing. In agreement with the hypothesis relating abnormal perception of novel information to sociocommunicative function, Gomot et al. (2008) demonstrated that abnormal brain responsivity of right middle frontal gyrus to novel auditory stimulus was related to increased ASD symptomatology. The authors theorized that this increased activation may correspond to an over-focused attentional style, which would result in social impairments during dynamic social interactions.

Liss and colleagues (2006) hypothesized that over-reactivity may be a response to hyperarousal in ASD, and may result in this over-focused attentional style. In agreement with this prediction, Liss et al. (2006) demonstrated that the individuals with ASD that were hyperaroused and over-focused were the most socially impaired. The authors also predicted that over-focused attention in these individuals would result in an amplification of sensory information at the locus of attention. This hypothesis is congruent with the findings of Joseph et al. (2009). These authors reported that enhanced visual search ability (as measured by RT x set size y-intercepts) was related to increased sociocommunicative impairments in children

with ASD. That is, enhanced perceptual abilities, which may develop due to over-focused attention, are related to greater sociocommunicative impairment.

Orienting Network. Courchesne and colleagues (1994) hypothesized that early deficits in shifting and orienting attention may result in inability to follow and subsequently participate in reciprocal social interactions. As described above, impairments in disengaging attention are the earliest described attentional impairments in infants with ASD. Specifically, both Zwaigenbaum (2005) and Elsabbagh (2009) reported slowed disengagement in at-risk infants. Furthermore, Zwaigenbaum et al. (2005) reported that all infants who exhibited increased difficulties disengaging attention between 6 and 12 months received an ASD diagnosis at 24 month. Similarly, in an investigation of temperament in infants at-risk for ASD, infants that later receive a diagnosis of ASD exhibit low attentional shifting and greater difficult with attentional control (Garon et al., 2009).

Early impaired disengagement may be a possible primary disturbance that contributes to the manifestation of joint attention difficulties in ASD (see Charman, 2003, for review of joint attention difficulties in ASD). For example, Hood et al. (1998) demonstrated that while children are able to use gaze cues to direct visual attention if the cue remains on screen, difficulties disengaging attention may result in the absence of gaze-contingent orienting. In TD children, the ability to efficiently disengage attention develops after a period of obligatory (sticky) attention (at approximately 1 month of age). However, in at-risk infants who are later diagnosed with ASD, the manifestation of this disengaging impairment occurs at the time during which TD infants begin to exhibit joint attention behaviors (i.e., 6-12 months). Recently, Schietecatte and colleagues (2011) reported that children with ASD that disengaged attention faster made more joint attention initiations. This finding suggests that impaired joint attention abilities may develop due to dysfunction attentional disengagement, and has important implications for language and theory of mind development (as discussed above).

Concordantly, previous authors have hypothesized that language deficits in children with ASD may be related to an orienting deficit (Kinsbourne & Lempert, 1979). Prior studies have demonstrated that early joint attention abilities are related to later language abilities in children with ASD (Thurm, Lord, Lee, & Newschaffer, 2007). In agreement with both of these findings, Dawson and colleagues (2004) demonstrated that that joint attention abilities were related to language proficiency in children with ASD, and that social orienting contributed to language abilities via its relationship to joint attention.

Executive Control. Based on the research reviewed above, 3- to 4-year-old children do not demonstrate executive impairments, though they appear to develop later in childhood. Although executive deficits may contribute to the later manifestation of some sociocommunicative impairments in ASD, their absence in younger children with ASD suggest that they maybe a secondary impairment associated with ASD, and thus their relationship to the development of sociocommunicative deficits will not be discussed.

Outline of Dissertation

This introduction has reviewed the maturation of attention subcomponents in typical development, discussed prior research investigating these subcomponents in ASD, and outlined the role of attention in 1) the development of sociocommunicative functions, and 2) the development of sociocommunicative impairments in ASD. Next, four experimental chapters focused on examining attention in ASD and how atypical attentional processes are related to core ASD deficits in social and communication functions are presented. The study in Chapter 2 employed behavioral and eye-tracking measures to examine novelty processing in ASD and further, how sensitivity to new information was related to sociocommunicative impairments in ASD. Chapter 3 presents an investigation of the efficiency of all three attentional networks and how efficiency of each attentional network was associated with ASD symptomatology. Chapters 4 and 5 present studies of activation and connectivity of

attentional networks associated with visual search in ASD, and how behavioral and neural indices of search were related to deficits in social and communicative abilities in ASD. Following these experimental chapters, Chapter 6 integrates the findings from Chapters 2 through 5, discusses how the findings relate to the current body of literature of attention and ASD, examines how impairments in attention may relate to the development of ASD, and finally, discusses directions for future research endeavors.

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CHAPTER 2

Impaired Prioritization of Novel Onset Stimuli in Autism Spectrum Disorder

Abstract

Background: Deficiency in the adaptive allocation of attention to relevant environmental stimuli is an associated feature of autism spectrum disorder (ASD). Recent evidence suggests that individuals with ASD may be specifically impaired in attentional prioritization of novel onsets. **Method:** We investigated modulation of attention by novel onset stimuli in 22 children with ASD and 22 age- and IQ-matched typically developing (TD) children using a preview visual search task (Donk & Theeuwes, 2003). In preview search, a subset of search stimuli (old) is presented briefly before the remaining stimuli (new) with the effect that search times for targets appearing among the new elements are typically shorter than for those appearing among the old elements. **Results:** Whereas the TD group exhibited faster reaction time (RT) to targets occurring as novel search elements, the ASD group performed similarly in target new and old conditions, indicating impaired attentional prioritization of novel onsets. Group differences in eye-movement behavior, including fixation frequency and saccadic error for novel onset stimuli, were consistent with the RT findings. Attentional modulation by novel onsets varied inversely with social-communicative symptom severity in the ASD group. **Conclusions:** The results provide further evidence of reduced sensitivity to novel onsets in ASD, and suggest that impaired processing of dynamic stimuli, possibly associated with abnormalities in the dorsal visual processing stream, may be implicated in the core symptoms of ASD.

Although autism is diagnosed on the basis of impairments and anomalies in three core symptom domains, namely, communication, reciprocal social interaction, and repetitive and stereotyped interests and behaviors, abnormal modulation of attention is a well-documented associated feature of the disorder (Burack, Enns, Stauder, Mottron, & Randolph, 1997; Plaisted, 2000). Individuals with autism spectrum disorder (ASD) are often overly selective and focused in their attention (Burack, 1994; Mann & Walker, 2003) and are typically poor at allocating attention to relevant stimuli (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998).

Adaptive allocation of attention to relevant stimuli in the environment involves both *top-down* and *bottom-up* processes. Whereas top-down guidance of visual attention is voluntary and depends on task-relevant objectives represented in the mind of the observer, bottom-up control of visual attention is involuntary and is based on stimulus characteristics that are independent of the goals of the observer. Abrupt onset, as when a novel object suddenly appears where nothing was before, is one such stimulus characteristic and has been shown to be uniquely powerful in capturing attention (Jonides & Yantis, 1988).

In the first study to explicitly investigate attention to novel onsets in ASD, Greenaway and Plaisted (2005) found impaired modulation of attention by onset stimuli, but not by color stimuli, in two different experiments. The authors argued that a deficit in attentional prioritization of dynamic onsets was consistent with autistic deficits in processing social information, which is by nature dynamic and transient, and their findings converged with prior evidence of motion perception impairments implicating the dorsal visual processing stream in the neuropathology of autism (Milne et al., 2002; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005; Spencer et al., 2000).

Our goal in the present study was to further investigate attentional modulation by novel onsets in ASD specifically in the context of visual search. Given that individuals with

ASD tend to excel at visual search (e.g., O'Riordan & Plaisted, 2001; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001), further evidence of an onset-related deficiency in this domain would be particularly compelling. In visual search, an observer looks for a target stimulus among an array of distractor stimuli and responds whether a target is present or absent. To assess attentional prioritization of novel onsets in visual search, we used a preview visual search task developed by Donk and Theeuwes (2003). In this task, a subset of search elements ("old") is briefly presented prior to the appearance of the remaining search elements ("new"). When a target (blue H) is present, it either appears among the new distractors (blue As, green Hs) or, with equal probability, among the old distractors (also blue As, green Hs) through an isoluminant color change of an old element (green H to blue H) simultaneous with the presentation of the new elements. Using this paradigm, Donk and Theeuwes (2003) demonstrated that search times for new-element targets were significantly shorter than for old-element targets, indicating that new onsets were prioritized even though there was no benefit to task performance in doing so, and leading to the conclusion that the onset stimuli automatically captured the observers' attention.

In the present study, we administered Donk and Theeuwes preview search task to a group of children and adolescents with ASD. We reasoned that if participants with ASD are impaired in the attentional prioritization of novel stimuli, they would exhibit a reduced RT advantage for new over old targets in comparison to typically developing children and adolescents. In addition to examining the effects of the main experimental manipulation on RT, we tracked participants' eye movements during the entire search procedure to assess whether differences in looking behavior might accompany group differences in RT. As such, the eye-tracking data could provide an important source of convergent information on the modulation of attention by novel onsets. Finally, to evaluate Greenaway and Plaisted's (2005) suggestion that deficiencies in processing transient stimuli may be linked to social-

communicative symptoms in ASD, we examined associations between sensitivity to novel onsets and a behavioral observational measure of autism symptom severity. Evidence linking a specific attentional impairment to the core social-communicative symptoms in ASD would raise the possibility that deficits in attention modulation are not merely associated or secondary features of autism, but are of deeper etiological significance with regard to the defining symptoms of ASD and their neurobiological underpinnings.

Methods

Participants

Participants were 22 school-age children and adolescents with ASD (19 males), all of whom were judged to meet DSM-IV criteria for autism or PDD-NOS by an expert clinician (second author), and an age-matched comparison group of 22 typically developing (TD) children (18 males). Clinical diagnoses were confirmed with the Autism Diagnostic Interview – Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) and the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999). All children in the ASD group met diagnostic criteria for autism on the ADI-R, with the exception of two children who were one point below the diagnostic threshold in the repetitive behavior domain. On the ADOS, 17 children met criteria for a classification of autism, two met criteria for a classification of autism spectrum disorder (or PDD-NOS), and three met ADOS criteria for autism in the social domain, but were below threshold in the communication domain. The latter three children met full criteria for autism on the ADI-R. The ASD and TD groups were well-matched on age (ASD: M = 14;1, SD = 2;11; TD: M = 14;4; SD = 2;8; t (42) = 0.2, p = .82) and on nonverbal IQ (ASD: M = 109, SD = 11; TD: M = 109, SD = 13; t (42) = 0.0, p = .96, but not on verbal IQ (ASD: M = 104, SD = 19; TD: M = 113, SD = 16; t (42) = 1.7, p < .10), as measured with the Kaufman Brief Intelligence Test – II (Kaufman & Kaufman, 2004). Informed consent was

obtained from all research participants in accordance with the Boston University Medical Campus IRB.

Apparatus

The experiment was presented using E-Prime 1.1 software on a Pentium IV 3.2 GHz PC with a 19-inch LCD (refresh rate of 75 MHz). Test responses were registered using a PST serial response button box. Participants' point of regard was monitored using an ISCAN Model ETL-500 head-mounted, pupil-corneal reflection tracking system that allowed participants to move their heads freely during the test procedure.

Stimuli

The target was a blue capital H and the distractors were green Hs and blue As drawn in isoluminant blue (22.3 cd/m²) and green (22.8 cd/m²) and displayed on a darker (11.3 cd/m²) gray background. At a viewing distance of 57 cm, each search element subtended a visual angle of 0.7° x 0.85°, and was randomly positioned on a 6 x 6 array of 2.2º x 2.2º squares. Elements were randomly positioned within each square to produce layout irregularity. Either 6, 10, or 14 distractors, half green Hs and blue As, appeared in the *preview frame* (old elements) for 400 ms, after which the remaining 14 elements appeared in the *onset frame* (new elements). When a target was present, it occurred with equal probability as a new or as an old element, in which case a blue H replaced a green H when the onset frame appeared. See Figure 1.

[FIGURE 2.1]

Design

The experiment consisted of 192 trials, divided into 4 blocks. A target was present on half of the trials. Within each block, target presence (present, absent), target occurrence (as old element, as new element) and set size (20, 24, 28) were varied in pseudorandom order.

Procedure

The task was to respond via a dominant-hand, two-choice, button-box response as to whether a target was present or absent. Each trial began with a fixation cross presented alone for 1000 ms. With the cross remaining on the screen, the preview and onset stimuli were presented in succession. The stimuli remained on the screen until the participant responded or 7000 ms had elapsed. Participants were informed that the target appeared with equal frequency among the old and new elements and were instructed to respond as quickly as possible without making errors. Demonstration trials and 24 practice trials were administered with corrective feedback.

Results

In all RT analyses, medians were used to reduce the influence of outliers. In all figures, error bars represent one standard error of the mean.

Search Performance

Error. A mixed-model ANOVA with the factors group, target presence, and set size was conducted on the raw error data. As can be seen in Figure 2, error was higher for present than absent trials, $F(1, 42) = 93.2$, $p < .001$, $\eta_p^2 = .69$, and increased with set size, $F(2, 84) = 4.6$, $p < .02$, $\eta_p^2 = .10$. There was no group difference in error rate, $F(1, 42) = 0.2$, nor were there any group interaction effects. A separate analysis including only present trials also showed no group differences in error between the target old and new conditions, $F(1, 42) = 0.03$. Correlational analyses revealed no speed-accuracy tradeoffs in either group.

[FIGURE 2.2]

Reaction time. A similar ANOVA was conducted on median RT for correct trials. As illustrated in Figure 3, RT was longer in target absent than target present trials, $F(1, 42) = 316.0$, $p < .001$, $\eta_p^2 = .88$, and increased as a function of set size, $F(2, 84) = 35.4$, $p < .001$, $\eta_p^2 = .46$. Both of these effects on RT (as well as on error) were expected based on the visual

search literature. There was no main effect of group, $F(1, 42) = 0.2$, nor were there any group interaction effects. An additional ANOVA that included only target present trials showed that RT was faster when targets appeared as new elements than when they appeared as old elements, $F(1, 42) = 10.7$, $p < .01$, $\eta_p^2 = .20$, and that RT increased with set size, $F(2, 84) = 9.9$, $p < .001$, $\eta_p^2 = .19$. There was no main effect of group, $F(1, 42) = 1.1$, but there was a group X target occurrence interaction, $F(1, 42) = 9.5$, $p < .01$, $\eta_p^2 = .19$. Analysis of this interaction showed that the ASD group performed marginally faster than the TD group in the target old condition, $F(1, 42) = 3.6$, $p < .06$, $\eta_p^2 = .08$, but that the groups did not differ in the target new condition, $F(1, 42) = 0.0$.

[FIGURE 2.3]

Repeated measures ANOVAs conducted separately for each group addressed the critical issue of whether participants obtained an RT benefit in the target new condition. Whereas the TD group showed a sizeable RT advantage when targets were new relative to when they were old, $F(1, 21) = 18.3$, $p < .001$, $\eta_p^2 = .47$, the autism group performed similarly in the two conditions, $F(1, 21) = 0.02$. See Figure 4a.

[FIGURE 2.4]

Search slopes. The slope of the function relating median RT to set size reflects the RT cost (ms/item) of each additional distractor and is generally taken as a measure of search efficiency, with steeper slopes indicative of slower, less efficient search. Attentional prioritization of new elements would be expected to yield significantly shallower slopes for targets appearing among the new elements than those appearing among the old elements. In contrast, slopes would not be expected to differ between target old and new conditions for children who fail to prioritize novel onsets. In fact, for both groups, search slopes were shallower in the target new condition (ASD: 5.7, TD: 11.2) than in the target old condition

(ASD: 26.5, TD: 34.5), $F(1, 42) = 5.9$, $p < .05$, $\eta_p^2 = .12$. These effects did not differ significantly between groups.

Eye-Movement Behavior

Eye-movement data were successfully collected for 19 of the 22 ASD participants and all TD participants. For the 400 ms preview frame, there were no differences between groups or between target old and new conditions for number of fixations per trial ($M = 1.1$) or mean fixation duration ($M = 608$ ms). The remaining analyses focused on eye movements during the onset frame for target present trials in order to determine if there were any group differences in looking behavior related to the target occurrence condition. One set of analyses examined fixations made anywhere in the search display, and included measures of fixation frequency and duration as well as latency and error of the first saccade. Additional analyses were conducted to examine differences in fixation frequency specifically to old versus new elements and to blue versus green elements.

Fixation frequency and duration. To count as a fixation, point of regard had to be maintained for at least 5 continuous data samples (80 – 85 ms at a sample rate of 60 Hz) within an area of 1° of visual angle. There was no main effect of group on fixation number, $F(1, 39) = 1.6$, but there was a marginally significant group x target occurrence interaction, $F(1, 39) = 3.7$, $p < .06$, $\eta_p^2 = .09$. Whereas the ASD group made an equal number of fixations on target old ($M = 2.8$) and target new ($M = 2.8$) trials, TD participants made more fixations on target old ($M = 3.3$) than target new ($M = 2.9$) trials, which was mirrored by their increased RT for the target old condition. There were no differences between groups, $F(1, 39) = 2.1$, or between old and new target conditions, $F(1, 39) = .02$, in fixation duration ($M = 331$ ms).

Latency and error of first saccade. Latency of first saccade was measured as the duration between the start of the onset frame and the time at which the first saccade was initiated. There were no group, $F(1, 39) = 0.3$, or other effects on latency of first saccade.

Error of first saccade was measured as the distance between the first fixation on the onset frame and the target location. There was no main effect of group on saccade error, $F(1, 39) = 0.6$, but there was a significant interaction between group and target occurrence, $F(1, 39) = 5.2$, $p < .05$, $\eta_p^2 = .12$, as illustrated in Figure 4b. A repeated measures ANOVA conducted separately for the TD group showed a main effect of target occurrence, $F(1, 21) = 8.4$, $p < .01$, $\eta_p^2 = .29$, with decreased saccade error in the new condition. A similar analysis showed no difference between conditions in the ASD group, $F(1, 18) = 0.1$. This interaction mirrored the group X target occurrence interaction found for RT, as can be seen by comparing Figures 4a and 4b.

Fixations to old versus new elements. On each trial, there were either 6, 10, or 14 old elements and 14 new elements. For each fixation, we determined whether the closest element (within 2°) was old or new. As illustrated in Figure 5, in the target old condition, the ASD group made significantly fewer fixations than the TD group to old elements, $F(1, 39) = 4.3$, $p < .05$, $\eta_p^2 = .09$, and new elements, $F(1, 39) = 5.2$, $p < .05$, $\eta_p^2 = .12$. In contrast, in the target new condition, the groups did not differ in number of fixations to either old or new elements. These findings reflected the group differences in RT between the target old and new conditions.

A more informative comparison with regard automatic prioritization of onset stimuli was the extent to which participants fixated new elements when the target was not present among them as compared to when it was. Within-group comparisons showed that the TD group fixated new elements in the old condition significantly more than they did in the new condition, $F(1, 21) = 6.7$, $p < .02$, $\eta_p^2 = .24$, suggesting that attentional prioritization of novel onsets contributed to their longer RT when targets were among the old stimuli. In contrast, the ASD group fixated new elements in the target old condition no more than in the target new condition, $F(1, 18) = .01$.

[FIGURE 2.5]

Fixations to blue versus green elements. Because top-down, feature-based inhibition of old elements has been argued to facilitate attentional prioritization of new elements in preview search (Olivers, Humphreys, & Braithwaite, 2006), we analyzed fixations by stimulus color in order to assess possible group differences in inhibitory guidance of attention. This analysis revealed that participants were much more likely to direct attention to blue elements, which could be a target, than to green elements, which could never be a target, $F(1, 39) = 142.6$, $p < .001$, $\eta_p^2 = .79$. Whereas participants with ASD made fewer fixations per trial to blue stimuli than TD participants (ASD: $M = 1.0$, TD: $M = 1.3$), $F(1, 39) = 4.2$, $p < .05$, $\eta_p^2 = .10$, consistent with their overall lower frequency of fixations, the number of fixations to green stimuli did not differ between the groups (ASD: $M = 0.5$, TD: $M = 0.5$), $F(1, 39) = 0.3$. These findings indicated that feature-based inhibition of attention to green elements was strongly at play in this preview search paradigm and did not differ between groups.

Search Behavior and Autism Symptom Severity

Sensitivity to novel onset stimuli was measured by subtracting median RT for the target new from the target old condition. Positive old-new difference scores reflected faster RT for new relative to old targets. Symptom severity in ASD participants was assessed with Module 3 of the ADOS (Lord et al.,1999). The ADOS involves a series of experimenter-administered social occasions and "presses" designed to provide quantitative observational ratings of communicative and social behaviors. Higher ADOS scores reflect increased symptom severity. Correlational analyses revealed that the old–new difference score was inversely related to communication, $r(20) = -.62$, $p < .01$, social, $r(20) = -.47$, $p < .05$, and combined communication and social, $r(20) = -.59$, $p < .01$, ADOS algorithm scores, demonstrating that decreased sensitivity to novel onsets was associated with increased

symptom severity in ASD participants. The old-new difference score was not significantly associated with the ADOS repetitive behavior algorithm score $r(20) = -.27$.

To ensure that the relation between novel onset sensitivity and symptom severity was independent of age and IQ, additional correlational analyses were conducted. The old-new difference score was not correlated with age, $r(20) = .01$, verbal IQ, $r(20) = .10$ or nonverbal IQ, $r(20) = .00$, all ps $> .60$, nor was ADOS social-communication score correlated with age, $r(20) = .02$, verbal IQ, $r(20) = .08$, or nonverbal IQ, $r(20) = .26$, all ps $> .20$. Further, in partial correlations controlling separately for the effects of age, verbal IQ, and nonverbal IQ, the correlations between the old-new difference score and ADOS scores all remained at the same p-values as in the raw correlations.

Discussion

Two main findings emerged from this study. First, children with ASD exhibited impaired attentional prioritization of novel onset stimuli in visual search, which was evident in both their RT data and eye-movement behavior. Second, decreased sensitivity to novel onsets was associated with more severe symptoms in children with ASD. We discuss each of these findings in turn.

In contrast to their TD peers, children with ASD showed no difference in RT to search targets occurring as new elements as compared to targets occurring as old elements, indicating that their attention was not preferentially directed to novel onsets. Further, the different patterns of RT between groups were paralleled by group differences in eye movement behavior. When a target occurred as a new element, accuracy of first fixations with respect to the target location improved in the TD group, suggesting that attention was directed to new elements in the search array. In contrast, saccade accuracy did not differ between the new and old conditions in the ASD group, again suggesting that individuals with ASD did not selectively attend to newly appearing elements in the search array. In addition, TD

participants made more fixations to new elements in the target old than in the target new condition, consistent with the conclusion that attentional capture by novel onsets lengthened their RT for old targets. In contrast, ASD participants fixated new elements no more in the target old than in the target new condition.

Greenaway & Plaisted (2005) previously reported impaired attentional modulation in children with ASD in tasks in which a single visual onset served as either a cue or a distractor for spatially allocating attention. Our results are in agreement with those of Greenway & Plaisted and extend them by demonstrating impaired modulation of attention by multiple novel onsets, in the context of a color-form conjunction task in which individuals with ASD typically excel (O'Riordan et al., 2001; O'Riordan and Plaisted, 2001), and by providing convergent eye-tracking evidence of differences in looking behavior in response to abrupt onsets in children with ASD. Together, these findings provide fairly compelling evidence of a specific anomaly of attention modulation that could explain a range of associated behavioral features of ASD, including tendencies toward over-selectivity and perseveration in attentional focus and weaknesses in orienting adaptively to relevant environmental stimuli. At a deeper level of explanation, it is also possible that impairments in attentional prioritization of dynamic stimuli could, as Greenaway and Plaisted (2005) have proposed, impede processing of social stimuli, which are by nature discontinuous and in continual flux. As such, impaired prioritization of onset stimuli may index neurocognitive differences in attention modulation that potentially contribute to the development of the social-communicative deficits that are essentially defining of ASD. Below, we consider this possibility further in relation to our finding of a link between onset sensitivity and ASD symptom severity.

Before turning to our second finding, we address some possible objections or caveats to our interpretation of the RT results from the preview search task. First, it could be argued that the lack of an RT benefit for ASD participants in the target new condition resulted not

from a failure to prioritize new stimuli, but more basically from a failure to de-prioritize or disengage from old stimuli (Landry & Bryson, 2004; Townsend, Courchesne, & Egaas, 1996). However, if this were the case, we would have expected to find a reversal of the typical preview effect in ASD, with faster detection of old than of new targets. Moreover, if attentional disengagement were a problem for the ASD participants in this study, we would have expected them to exhibit longer saccade latencies than TD participants, and they did not.

Second, there remains considerable debate regarding the neurofunctional mechanisms underlying the preview effect in visual search (Donk, 2006; Olivers et al., 2006), with evidence of both top-down and bottom-up control of attention, in part determined by the specific experimental parameters used. In the present study, we were specifically interested in automatic, bottom-up modulation of attention by dynamic stimuli in ASD. We therefore used a paradigm that specifically minimized the influence of voluntary, top-down inhibition of attention to old elements (Watson & Humphreys, 1997) by making inhibitory marking of old elements task-irrelevant, in so far as targets were as likely to appear among old as among new elements. Although we cannot rule out definitively that weaknesses in top-down inhibitory control contributed to the failure of participants with ASD to prioritize new search elements, our eye-tracking analyses indicated that ASD participants were able to exercise strategic inhibition of attention, based on stimulus color, equally as well as TD participants. Further, in prior studies of negative priming, individuals with autism have been shown to have normal top-down attentional inhibition based on stimulus location (Brian, Tipper, Weaver, & Bryson, 2003) and stimulus identity (O'Riordan, 2000). These findings suggest that insensitivity to novel onsets in our ASD participants did not derive from an impairment of top-down inhibitory processes.

Finally, we found that children with ASD, like TD children, exhibited significantly shallower RT x set size slopes in the target new than in the target old condition. If children

with ASD were insensitive to the onset of new elements, their slopes would not be expected to differ significantly between new and old conditions. Shallower slopes in the new condition could thus be taken as evidence that ASD participants, like our TD participants and healthy adults in other studies (Donk & Theeuwes, 2003), selectively prioritized the new elements, making their search times relatively constant and independent of the number of old elements. However, inspection of the RT data suggests that the slope data may be misleading in this regard. For example, if participants with ASD prioritized novel onsets, it would be difficult to explain why their RT for new targets was slower than for old targets at the set size of 20 and no faster than for old targets at the set size of 24 (see Figure 3). In contrast, TD participants exhibited consistently faster RT for targets appearing as new elements across all set sizes in addition to a shallow RT x set size slope for the target new condition. Another consideration is the degree to which color-based inhibition may contribute to the differences in slopes between target new and target old conditions in the preview search paradigm we administered. Even in the absence of attentional prioritization of novel onsets, inhibition of attention to green elements, which was found to be operative in both groups, would be expected to result in decreased search efficiency in the target old relative to the target new condition. This is because color-based inhibition would lead participants to search among all of the blue elements before re-attending to the previously green element which becomes a target in the old condition. In contrast, in the new condition, inhibition of green elements leads to relatively more efficient discrimination of a novel blue target. Thus, feature-based inhibition may have been at least partly responsible for shallower slopes in the target new condition in both groups.

Children with ASD not only exhibited impaired sensitivity to abrupt onsets, but severity of social-communicative symptoms within the ASD group varied inversely in relation to onset sensitivity. In other words, the less attentionally responsive children were to abrupt

onsets the more impaired they were in their social-communicative functioning, and vice versa. A particular strength of our measurement of onset sensitivity was that as a difference score it was independent of absolute level of processing efficiency, which could reasonably be expected to covary in a non-specific way with the degree of impairment in ASD or any behaviorally defined disorder. In a similar vein, the correlation between attention modulation by onsets and symptom severity was independent of IQ as well as age.

Evidence that impaired processing of dynamic onsets is directly related to symptom severity suggests that a basic attentional deficit, not specific to the social domain, could have explanatory power with regard to the causes and development of autistic social-communicative impairment, as Greenaway and Plaisted (2005) hypothesized. How might this link between an impairment in attention modulation and autism symptom severity be explained in terms of brain-level processes? As noted in the introduction, prior research has implicated the dorsal visual processing stream in the neuropathology of autism. Although there is considerable controversy as to the exact nature of the dorsal visual stream and associated motion processing impairments in autism, they appear to affect higher-level dorsal stream functions (Bertone et al., 2005; Dakin & Frith, 2005; Pellicano et al., 2005). These include non-social (or domain-general) processing functions earlier in the dorsal visual stream typically associated with human MT/V5, such as motion coherence detection (Milne et al., 2002; Pellicano et al., 2005; Spencer et al., 2000), as well as functions with profound social significance that are further down the dorsal visual stream and specifically associated with the superior temporal sulcus, such as perception of biological motion (Blake, Turner, Smoski, Pozdol, & Stone, 2003) and of eye gaze direction (Pelphrey, Morris, & McCarthy, 2005). This raises an intriguing question: Do domain-general abnormalities in attention modulation interfere with the development of higher-level social-information processing skills in autistic children over time, or do processing deficits for social and non-social stimuli reflect a

common ontogenetic disturbance in brain formation that affects contiguous areas of dorsal visual cortex. Longitudinal behavioral research with young children at risk for autism complemented by pediatric neuroimaging studies will help to resolve these questions. Such research can tell us whether domain-general attentional abnormalities are causal or corollary in the development of autistic social-communicative deficits.

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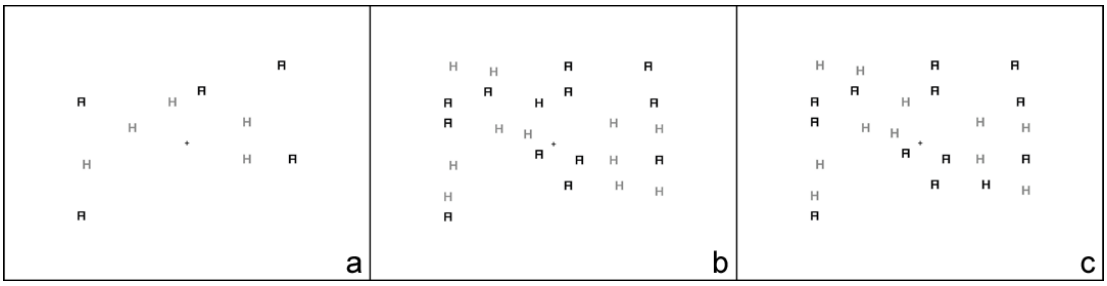

Figure 2.1. Illustration of target present trials. The preview frame was displayed for 400ms (a) after which the onset frame appeared with a target at an old stimulus location (b) or a target occupying a new spatial location (c). Blue stimuli are represented in black and green stimuli in gray.

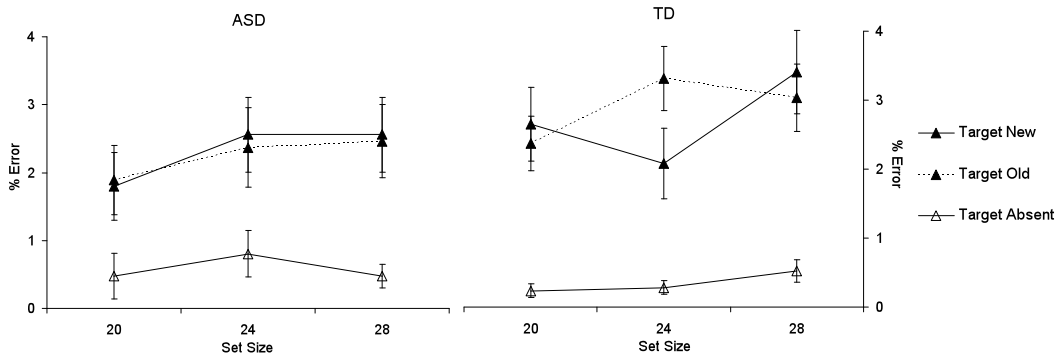

Figure 2.2. Percent error as a function of group, target presence, target occurrence, and set size.

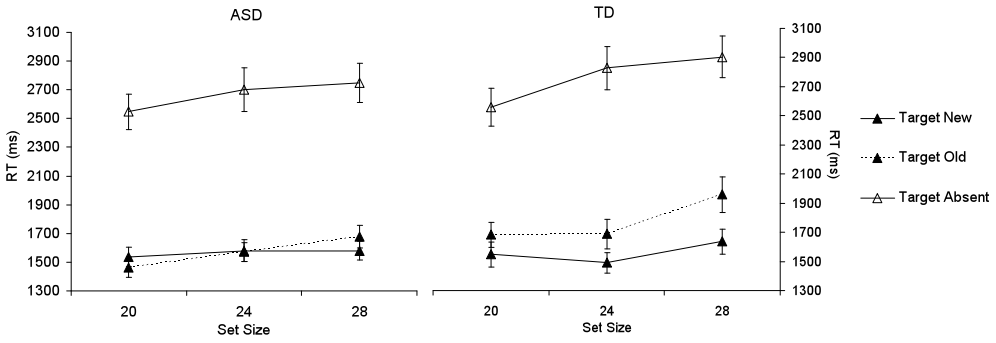

Figure 2.3. Median RT as a function of group, target presence, target occurrence, and set size.

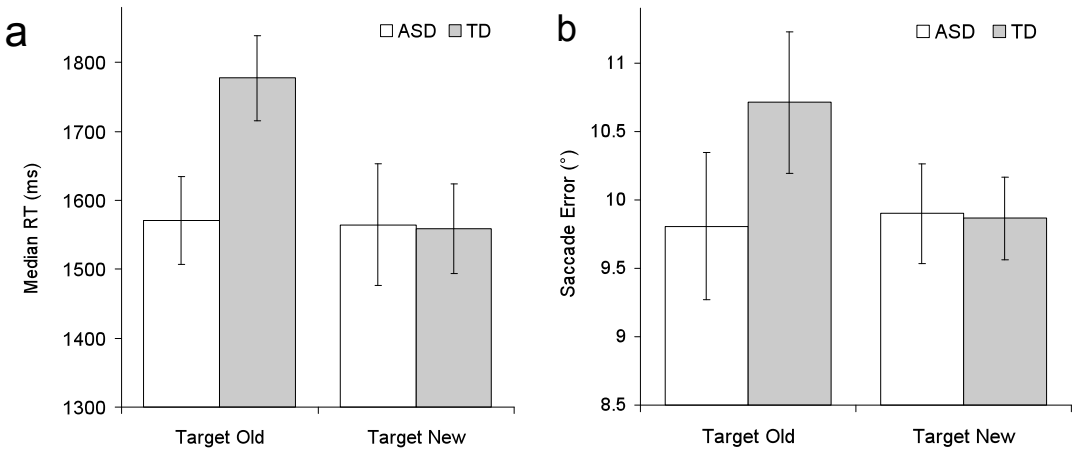

Figure 2.4. Median RT (a) and mean error of first saccade (b) on target present trials.

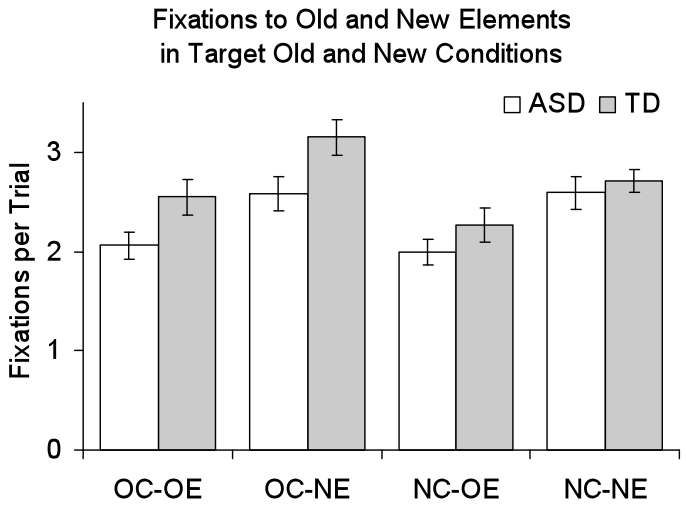

Figure 2.5. Number of fixations to old and new elements on target old and target new trials. OC-OE: target old condition/fixation on old element; OC-NE: target old condition/fixation on new element. NC-OE: target new condition/fixation on old element; NC-NE: target new condition/fixation on new element.

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CHAPTER 3

Attentional Networks in Children and Adolescents with Autism Spectrum Disorder

Abstract

Background: Individuals diagnosed with autism spectrum disorder (ASD) exhibit life long abnormalities in the adaptive allocation of visual attention. The ubiquitous nature of attentional impairments in ASD has led some authors to hypothesize that atypical attentional modulation may be a factor in the development of higher-level sociocommunicative deficits. **Method:** Participants were twenty children with ASD and twenty age- and Nonverbal IQ-matched typically developing (TD) children. We used the Attention Network Test (ANT) to investigate the efficiency and independence of three discrete attentional networks: alerting, orienting, and executive control. Additionally, we sought to investigate the relationship between each attentional network and measures of sociocommunicative symptom severity in children with ASD. **Results:** Results indicate that the orienting, but not alerting or executive control, networks may be impaired in children with ASD. In contrast to TD children, correlational analyses suggest that the alerting and executive control networks may not function as independently in children with ASD. Additionally, an association was found between the alerting network and social impairment and between the executive control network and IQ in children with ASD. **Conclusions:** The results provide further evidence of an impairment in the visuospatial orienting network in ASD and suggest that there may be greater interdependence of alerting and executive control networks in ASD. Furthermore, decreased ability to efficiently modulate levels of alertness was related to increased sociocommunicative deficits suggesting that domain-general attentional function may be associated with ASD symptomatology.

Individuals diagnosed with autism spectrum disorder (ASD) exhibit early (Elsabbagh et al., 2009; Osterling, Dawson, & Munson, 2002; Swettenham et al., 1998; Zwaigenbaum et al., 2005) and pervasive (see Allen & Courchesne, 2001; Burack, Enns, Stauder, Mottron, & Randolph, 1997, for reviews) abnormalities in the allocation of visual attention. The ubiquitous nature of attentional impairments in ASD has led some authors to hypothesize that early atypical attentional modulation may, in part, act as a significant contributing factor in the development of higher-level sociocommunicative deficits (Belmonte & Yurgelun-Todd, 2003; Dawson & Lewy, 1989; Gold & Gold, 1975; Ornitz, 1988; Pierce, Glad, & Schreibman, 1997).

Recently, Fan and Posner (2004) proposed conceptualizing attention as an organ system. This system is comprised of three specialized neurofunctional networks, previously described by Posner and Petersen (1990), which are responsible for a distinct set of cognitive processes: the alerting, orienting, and executive control networks. The authors hypothesize that this conceptualization may assist in elucidating differences in attentional modulation between typically developing (TD) individuals and individuals with atypical attentional processes. Evidence from behavioral, neuropsychological, and neuroimaging investigations now support the theory of separable anatomical networks responsible for unique sets of attentional functions (see Raz & Buhle, 2006, for a review); however, interactions between these networks are also important for successful and efficient attentional modulation in TD adults (Callejas, Lupianez, Funes, & Tudela, 2005; Callejas, Lupianez, & Tudela, 2004; Fan et al., 2009)

The alerting network is responsible for achieving and maintaining a state of increased sensitivity to incoming information. Alertness has been divided into tonic and phasic components (see Sturm & Willmes, 2001, for review). Tonic alertness is a state of general wakefulness; endogenously-controlled tonic alertness (referred to as vigilance or sustained

attention) is the voluntary maintenance of alertness at a certain level. Phasic alertness is a more transient alert state, modulated by a warning that precedes a target stimulus. The orienting network is responsible for the selection of information from sensory input. Orienting visual attention has been defined as disengaging, shifting, and reengaging attention (Posner, Walker, Friedrich, & Rafal, 1984). Finally, the executive control network is a multidimensional attentional system, responsible for inhibition, conflict resolution, planning, and cognitive flexibility.

Abnormal function of each attentional network has been demonstrated in ASD. Furthermore, specific deficits in alerting (Gold & Gold, 1975; Dawson & Lewy, 1989), orienting (Ornitz, 1988), and executive control (Ozonoff, Pennington, & Rogers, 1991) have been hypothesized to contribute to the development of ASD. Prior research on alertness / arousal in ASD has been inconsistent; individuals with ASD exhibit intact endogenous tonic (Garretson, Fein, & Waterhouse, 1990; Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998) and phasic (Raymaekers, van der Meere, & Roeyers, 2006) components of alerting, yet also demonstrate atypical arousal (e.g. Anderson & Colombo, 2009; Hirstein, Iversen, & Ramachandran, 2001) and reduced sensitivity to novel information (e.g. Ciesielski, Courchesne, & Elmasian, 1990; Keehn & Joseph, 2008).

Dysfunctional shifting and disengagement of attention has also been reported in ASD. Dawson and colleagues (1998) demonstrated that children with ASD have difficulties orienting to both social and non-social information within their environment. Previous studies using the Posner cueing paradigm (1980) have shown that individuals with ASD have difficulties disengaging (Wainwright-Sharp & Bryson, 1993) and shifting visual attention (Townsend et al., 1999; Townsend, Harris, & Courchesne, 1996), and demonstrate atypical activation of the orienting network (Haist, Adamo, Westerfield, Courchesne, & Townsend, 2005). Furthermore, studies employing the gap-overlap paradigm, a task used to evaluate

attentional disengagement by examining the RT differences to targets appearing with and without a central fixation, have also demonstrated that children with ASD evidence significant impairments in disengaging visual attention (Elsabbagh et al., 2009; Landry & Bryson, 2004).

Finally, the extant literature on executive control abilities in ASD suggests intact inhibitory processing (Lopez, Lincoln, Ozonoff, & Lai, 2005; Ozonoff & Strayer, 1997), but impaired cognitive flexibility (Courchesne et al., 1994; Ozonoff, Strayer, McMahon, & Filloux, 1994). Additionally, there appears to be a relationship between IQ and executive abilities in individuals with ASD (Liss et al., 2001; Lopez et al., 2005).

Together, these findings indicate that individuals with ASD exhibit impairments in each attentional network; however, no study has attempted to examine each attentional network in the same cohort of children. The Attention Network Test (ANT; Fan et al., 2002), which consists of both a cued reaction time task (Posner, 1980) and a flanker paradigm (Eriksen & Eriksen, 1974) permits investigators to examine each attentional network in the context of a single integrated task. The test, which was designed to be short and simple, has been used in TD children and adults (Fan et al., 2002; Rueda et al., 2004), as well as clinical populations with attentional abnormalities (for example see Johnson et al., 2008; Urbanek et al., 2009). To date, no study has employed the ANT to investigate attention networks in ASD. Our goal in the current study was to use the ANT to simultaneously examine alerting, orienting, and executive control networks in children and adolescents with ASD. Moreover, because it has been suggested that abnormalities in the modulation of attention may be related to sociocommunicative deficits, we sought to examine the relationship between attentional function and sociocommunicative impairments in children with ASD.

Methods

Participants

Twenty children and adolescents with ASD (19 males), all of whom met DSM-IV-TR (APA, 2000) criteria for an ASD (Autistic Disorder = 9; Asperger's Disorder = 11), and an age- and nonverbal IQ-matched comparison group of twenty typically developing (TD) children and adolescents (19 males) were included in the present study. Clinical diagnoses were confirmed using the Autism Diagnostic Interview – Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), and expert clinical judgment (author AJL). Children with ASD-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis) were excluded.

Per parent-report, participants in the TD group had no family history of ASD and were free of ASD-related symptoms or any other neurological or psychiatric conditions. Independent-samples *t*-tests confirmed that groups were matched on age, $t(38) = 0.4$, $p = .72$, and nonverbal IQ, $t(38) = -0.7$, $p = .49$, as determined by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999; see Table 1). Informed consent was obtained from all participants in accordance with the University of California, San Diego and San Diego State University Institutional Review Boards.

[TABLE 3.1]

Apparatus

The experiment was presented using Presentation software (nbs.neuro-bs.com) on a 1.83 GHz/1GB PC with a 19-inch CRT monitor. Participants were seated approximately 57cm from the monitor. Responses were recorded with a Cedrus (Model RB-420) button-box device.

Stimuli

Stimuli consisted of a central target, an arrow pointing left or right, flanked on each side by bars without arrowheads (neutral condition) or arrows either pointing in the same

direction (congruent condition) or the opposite direction (incongruent condition) (See Figure 1a). Stimuli were black and displayed on a gray background. Each arrow subtended a visual angle of 0.6° x 0.25° and was separated by neighboring arrows by 0.1°. The entire row of stimuli thus subtended a visual angle of 3.4°. The cue was an asterisk subtending 0.41° x 0.41° visual angle, and appeared directly over fixation cross (center cue), 1.2° above *and* below the fixation cross (double cue), or 1.2° above *or* below fixation cross (spatial cue) (see Figure 1b).

Design

The experiment consisted of 288 trials, divided into three blocks of 96 trials. Within each block, cue (no cue, center, double, spatial [all valid]), and flanker (neutral, congruent, incongruent) were varied in pseudorandom order.

Procedure

The participants' task was to indicate whether the center arrow pointed left or right via a button box response using the index and middle fingers of their dominant-hand. Each trial lasted 4000ms and began with a fixation cross presented alone for a variable duration (400-1600 ms). With the fixation cross remaining on the screen, a cue (no cue, center, double, spatial [all valid]) appeared for 100 ms. Following the cue there was a fixation period (fixation cross presented alone) for 400 ms. Subsequent to the fixation period, the target and flankers appeared above or below the fixation cross and remained on the screen until the participant responded or 1700 ms had elapsed. A post-target fixation period then appeared for a duration equal to 3500ms minus the duration of the initial fixation and RT (see Figure 1c). Twenty-four practice trials were administered with feedback before the start of the experimental trials.

Prior to beginning the experiment participants were told they were going to play the "stars and arrows" game. They were instructed to press the left button if the middle arrow pointed left or the right button if the middle arrow pointed right, regardless of which stimuli

appeared next to the center arrow (congruent, incongruent, neutral). Participants were told that sometimes stars would appear to tell them *when* or *when and where* the arrows would appear. Stars in the center or above *and* below were explained as cues to inform participants *when* the arrows would appear, whereas stars above *or* below were explained as cues to inform participants *when* and *where* the arrows would appear. Finally, participants were told to respond as quickly as possible without making errors.

[FIGURE 3.1]

Results

Error

Mean error rates were entered into a mixed-model repeated measures ANOVA with between-subject factor group (ASD, TD) and within-subject factors cue (no, center, double, spatial) and flanker (neutral, congruent, incongruent). As shown in Figure 2, there were main effects of cue, $F(3, 114) = 4.7$, $p < .01$, $\eta_p^2 = .11$, and flanker, $F(2, 76) = 12.1$, $p < .01$, $\eta_p^2 = .24$. Importantly, there was no difference for the mean error rate between the ASD (3%) and TD (3%) groups, nor were there any significant interactions between group and any factor (ps $> .3$).

[FIGURE 3.2]

Response Time

Median response times (RT) for correct trials were entered into mixed-model repeated measures ANOVA with between-subject factor group (ASD, TD) and within-subject cue (no, center, double, spatial) and flanker (neutral, congruent, incongruent). As illustrated by Figure 2, there was a main effect of cue, $F(3, 114) = 114.5$, $p < .01$, $\eta_p^2 = .75$, reflecting accelerated RT to spatial cues compared to no, center, and double cue conditions and faster RT to center and double cue compared to the no cue condition. In addition, there was a main effect of flanker, $F(2, 76) = 194.5$, $p < .01$, $\eta_p^2 = .84$, reflecting faster RT to neutral and congruent

flankers compared to incongruent flankers. There was also an interaction between cue and flanker, $F(6, 228) = 8.7$, $p < .01$, $\eta_p^2 = .19$. These main effects and interaction were expected based on previous ANT findings (Fan et al., 2002).

There was no significant RT difference between groups, $F(2, 38) = 1.9$, $p > .1$, $\eta_p^2 = .05$, however there were marginally significant interactions of group and cue, $F(3, 114) = 2.5$, $p < .07$, $\eta_p^2 = .06$, and of group and flanker, $F(2, 76) = 2.7$, $p < .08$, $\eta_p^2 = .07$.

Alerting, orienting, and executive control scores were calculated as follows. The alerting score was calculated by subtracting median RT in the double cue condition from the no cue condition (collapsed across flanker conditions). The orienting score was calculated by subtracting median RT in the spatial cue condition from the center cue condition (collapsed across flanker conditions). Finally, the executive control score was calculated by subtracting median RT in the congruent flanker condition from the incongruent flanker condition (collapsed across cue conditions). As can been seen in Figure 3, there was no significant difference between groups for alerting (ASD: 42ms; TD: 44ms), $F(1, 38) = .02$, $p > .8$, $\eta_p^2 = .00$; however, orienting scores were significantly reduced in the ASD (M: 39ms) as compared to the TD (M: 66ms) group, $F(1, 38) = 8.5$, $p < .01$, $\eta_p^2 = .18$, indicative of more inefficient orienting in the ASD relative to TD children. The executive control score was greater in the ASD (M: 122) compared to the TD (M: 96) group, however this was not significant, $F(1, 38) = 3.2$, $p < .1$, $\eta_p^2 = .08$. These results remained the same when network scores were scaled to median RT for all cue conditions and when participants with below average IQ (<85) were removed. Although ANT studies commonly analyze difference scores, there has been some criticism of this method. Therefore we conducted comparable analyses using the median RTs in ANOVAs for each network to examine interactions between group and cue condition (alerting, orienting) or flanker condition (executive control). Results from these analyses support those from the difference score analyses. The interaction between group and cue was

significant for the orienting score, $F(1, 38) = 8.5$, $p < .01$, $\eta_p^2 = .18$, but not the alerting score, $F(1, 38) = .2$, $p > .8$, $\eta_p^2 = .00$, and the executive control score, $F(1, 38) = 3.2$, $p = .08$, $\eta_p^2 = .08$.

[FIGURE 3.3]

Network Score Correlational Analyses

Correlational analyses of attentional network scores were used to investigate the relationship between each network and 1) IQ, to determined if network efficiency is related to cognitive ability, 2) other attentional networks scores, to explore the independence of attentional networks, and 3) measures of ASD symptomatology, to examine the relationship between sociocommunicative impairment and network efficiency.

IQ. Correlational analyses revealed that for the ASD group neither the alerting nor the orienting score was related to verbal, nonverbal, or full scale IQ, all *ps* > .1. However, the executive control score was inversely related to verbal, $r(18) = -.67$, $p < .01$, nonverbal, $r(18) = -.65$, $p < .01$, and full scale IQ, $r(18) = -.71$, $p < .01$, demonstrating that lower IQs were associated with more inefficient executive control in children with ASD. Because the significant correlations in the ASD group could partially be due to greater IQ variability in this group, correlations were completed excluding all individuals with below average verbal and nonverbal IQ (as above). Correlation for the ASD group between executive control score and full scale IQ, $r(16) = -.5$, $p < .05$, remained significant, although weaker, with these individuals removed. For the TD group, there was no relationship between any attention network score and any IQ measure, all *ps* >.1.

Attentional networks. Correlational analyses between attention network scores in prior studies have demonstrated non-significant relationships between the three attentional networks in both children and adults (Fan et al., 2002; Rueda et al., 2004). Consistent with prior research, TD children in the current study showed no correlation between the alerting,

orienting, and executive control networks, all *ps* > .6. However in children with ASD, partial correlations controlling for IQ revealed a positive relationship between the alerting and executive control networks, $r(17) = .47$, $p < .05$, suggesting that these two networks may not function as independently in children with ASD. A between-group comparison of the magnitude of the alerting-executive control correlations revealed that the relationship between these networks was significantly greater in the ASD as compared to the TD group, $z_{rASD\text{-}rTD} = 1.69$, $p < .05$, one-tailed.

ASD symptom severity. The relationship between the efficiency of each attentional network and sociocommunicative impairment was assessed by correlating attentional network scores with algorithm scores from the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999). ADOS algorithm scores are comprised of quantitative observational ratings of communication and social behaviors that are acquired during a set of experimenter-administered social situations. Higher scores on the ADOS represent increased levels of ASD symptomatology. Partial correlations controlling for IQ between ADOS algorithm scores and attention network scores revealed a significant association between the alerting score and the Social domain score, $r(16) = .50$, $p < .05$. There were no other significant correlations between attention network scores and ADOS domain scores (see Table 2).

[TABLE 3.2]

Discussion

The aim of the present study was two-fold. Our first goal was to investigate the efficiency and independence of the alerting, orienting, and executive attentional networks in children and adolescents with ASD. Children and adolescents demonstrated decreased efficiency of the orienting, but not the alerting or executive control, network compared to their TD peers. Additionally, in contrast to TD participants in the current and previous studies, the ASD group evidenced increased interdependence between the alerting and executive control

networks. Second, based on previous hypotheses that attentional impairments may be related to ASD symptomatology we examined the relationship between the efficiency of each network and measures of sociocommunicative impairment in ASD. Correlations between attention network scores and ADOS scores revealed that decreased alerting efficiency was associated with greater ASD sociocommunicative impairment. Each of these findings will be discussed in turn.

Consistent with previous behavioral (Townsend et al., 1999; Townsend et al., 1996), electrophysiological (Townsend et al., 2001), and functional magnetic resonance imaging (fMRI) studies of orienting in ASD (Haist et al., 2005), we found that children with ASD exhibited impairments in orienting visual attention to non-social peripheral cues. The lower orienting score in the ASD as compared to the TD group suggests that the children with ASD benefited less from the information provided by the spatial cue relative to the central cue. Since the ANT does not include invalidly cued trials, task-related demands on disengagement are limited. Therefore, the finding of reduced orienting scores may indicate that children with ASD may have a slowed or impaired ability to *shift* visual attention towards cued locations. Adaptive allocation of visual attention and the ability to shift attention between individuals and objects within the environment may be crucial for cognitive development across many domains. Prior studies have demonstrated that children with ASD demonstrate fewer attentional shifts compared to TD and developmentally delayed children (Swettenham et al., 1998) and fail to orient to both social and nonsocial environmental stimuli (Dawson et al., 1998). These early orienting deficits could reflect an initial pathological process (Mundy & Crowson, 1997), which has important downstream consequences for joint attention abilities (Dawson et al., 2004) and later developing sociocommunicative skills.

Children with ASD did not differ from TD children in the efficiency of the alerting network. The alerting score is a product of both intrinsic and phasic alertness. Intrinsic

alertness is measured as the increase of RT to the no cue condition; phasic alertness is measured as the decrease of RT to double cue condition (Posner, 2008). Developmentally, greater alerting scores in TD children relative to adults reflect slower RT in the no cue condition, and, thus less efficient modulation of intrinsic alertness (Rueda et al., 2004). Our finding of equivocal alerting scores is consistent with prior findings of intact tonic (Garretson et al., 1990; Pascualvaca et al,, 1998) and phasic (Raymaekers et al., 2006) alertness. However, equivalent alerting efficiency may reflect a compensatory executive processing mechanism utilized by children with ASD (discussed below).

Additionally, while children and adolescents with ASD did not exhibit differences in efficiency of the executive control network compared to TD children, the efficiency of this network was related to IQ in the ASD but not the TD group. These findings are in agreement with previous studies, which have shown that inhibitory control is not impaired in ASD (Ozonoff & Strayer, 1997) and that executive function abilities in individuals with ASD are related to IQ (Liss et al., 2001).

Posner and Peterson's (1990) model of attentional networks and subsequent neuroimaging studies using the ANT (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) have demonstrated that an intrinsic network of brain areas is responsible for the modulation of each attentional network. Although the functions of these attentional networks are separable and relatively independent (Fan et al., 2002; Rueda et al., 2004), a significant interaction between cue and flanker conditions in the present study and in prior studies suggests that these networks do interact. Similar to prior studies, our TD group exhibited no significant correlations between attention network scores; however, the ASD group demonstrated a significant association between alerting and executive control networks. That is in the ASD group, more inefficient executive control (i.e. greater interference associated with incongruent flankers resulting in a higher executive network score) was related to more inefficient alerting

(i.e. increased cost of no cue relative to double cue condition resulting in an increased alerting score). The association between the alerting and executive control networks could represent compensatory processing in ASD. Children with ASD who have more intact and efficient executive control abilities may be able to more efficiently regulate levels of arousal, resulting in a greater interdependence between these networks. Alternatively, as a consequence of the dysregulation of arousal, which generates states of both hyper- and hypoarousal (e.g. Anderson & Colombo, 2009; Hirstein et al., 2001), individuals with ASD may recruit or rely on executive control mechanisms in order to regulate atypical arousal levels. As a result the networks modulating alertness and executive control may become more interdependent in ASD. Although speculative, one possibility is that this increased interdependence could result in reduced cognitive resources during periods when atypical arousal regulation is necessary, and may explain poorer response inhibition in states of high arousal in ASD (Raymaekers, van der Meere, & Roeyers, 2006).

Because previous authors have hypothesized a link between attentional dysfunction and sociocommunicative impairment in ASD, we examined the relationship between attention network scores and measures of sociocommunicative impairment in our ASD sample. The results of these correlations suggest that decreased efficiency of the alerting network is related to increased social impairment in children with ASD. Inefficient modulation of tonic alertness may correspond to dysfunctional attentional regulation characteristic of ASD. Individuals with ASD can be both hyper-focused or easily distracted. Greater sociocommunicative difficulties may result from poorer modulation of attention given the dynamic nature of social interactions. Although corollary, the results of the current study support previous theories that hypothesize that atypical alertness/arousal may be associated with the development of sociocommunicative impairments in ASD.

A potential concern regarding the present study is the wide range in participant age. Although the current study includes individuals aged 8 to 19 years, a previous ANT study examining the developmental changes of each network (Rueda et al., 2004) demonstrated little change in orienting scores from six year-old children to adults. The lack of age-related changes for the orienting score has been attributed to the absence of invalid cues, as discussed above, which reduces demands for attentional disengagement. An additional concern is related to the heterogeneity of IQ scores, specifically within the ASD group. To confirm that group-related differences did not result from inclusion of lower-functioning individuals participants with below average IQ were removed; between-group differences for orienting scores remained unchanged. Lastly, although the ANT is now a widely used measure, the use of subtraction scores may make the interpretation of between-group differences in the efficiency of networks difficult (Posner, 2008). However, our analyses using raw scores instead of difference scores, produced exactly the same results.

Future application of the child ANT (Rueda et al., 2004) with younger children or lower-functioning individuals with ASD may be able to provide more detailed information about the developmental differences of attention. Recently, Posner and Rothbart (2005) have suggested that early attentional interventions may be useful tool promoting cognitive and social development. Because children with ASD evidence early attentional impairment, attentional interventions targeted at atypical attentional networks may produce generalized improvement across multiple domains.

In summary, the current study has demonstrated inefficient modulation of the orienting network in children with ASD. In addition, while the TD group demonstrated relatively independent attentional networks, we found a relationship between alerting and executive control in children with ASD, suggesting that these networks may not function as independently in ASD. Finally, inefficiency of the alerting network was associated with

greater social impairment in children with ASD. Although alerting efficiency was not universally impaired in individuals with ASD, this finding indicates that within-group differences in domain-general attentional function may be related to individual variability of sociocommunicative function along the autism spectrum.

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Table 3.1. Participant characteristics.

	ASD (n = 20) M (SD) Range	TD (n = 20) M (SD) Range
Age	13;9 (3;1) 8;8 – 19;11	13;5 (2;10) 8;11 – 18;10
Verbal IQ	108 (18) 80 – 147	111 (10) 87 – 134
Nonverbal IQ	111 (15) 76 - 140	113 (10) 96 – 132

Table 3.2. Correlations between attention networks and Autism Diagnostic Observation Schedule algorithm scores.

	Communication	Social	Total	Repetitive Behaviors
Alerting	.04	**.50***	.39	-.07
Orienting	.10	-.22	-.13	.14
Executive Control	.30	.28	.34	-.19

* $p < .05$

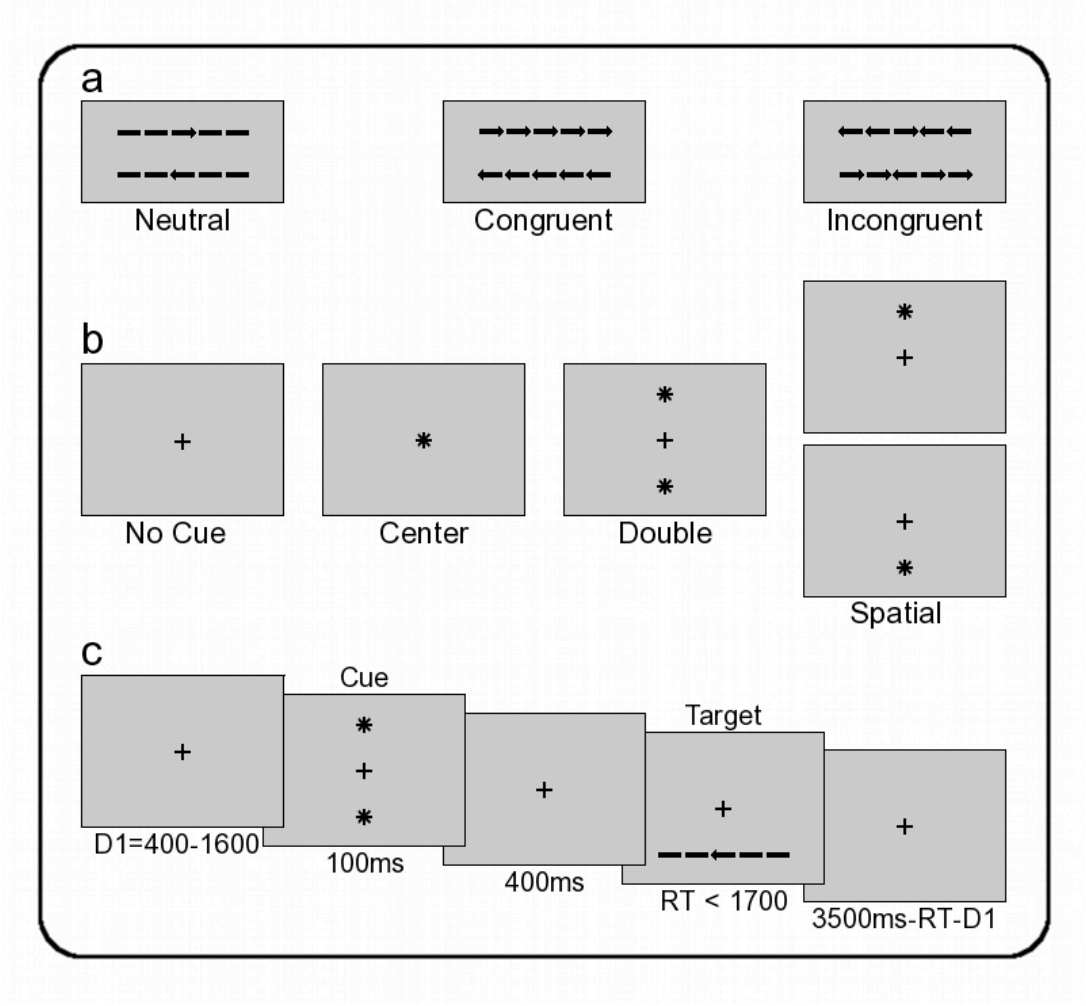

Figure 3.1. Illustration of Attention Network Test. Examples of flanker types (a), cue types (b), and the sequence and timing of a single trial (double cue neutral flanker condition displayed) (c).

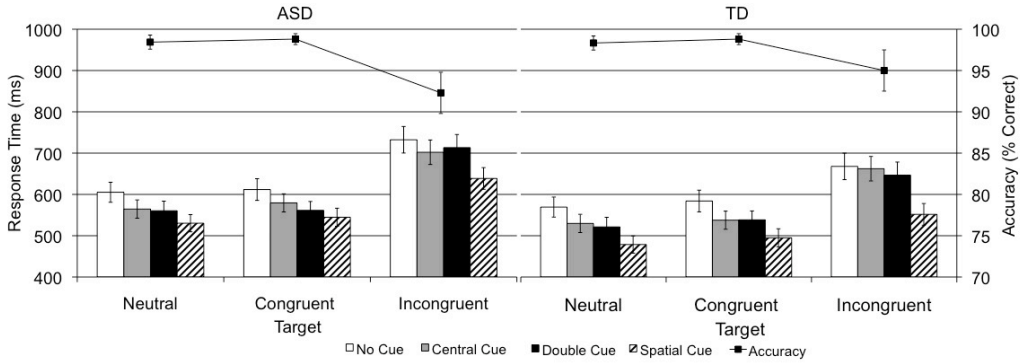

Figure 3.2. Bar graphs correspond to median response time (left axis) for correct trials only as a function of group, flanker, and cue. Line graphs correspond to average accuracy rates (right axis) as a function group and flanker (collapsed across cue). Error bars represent one standard error of the mean.

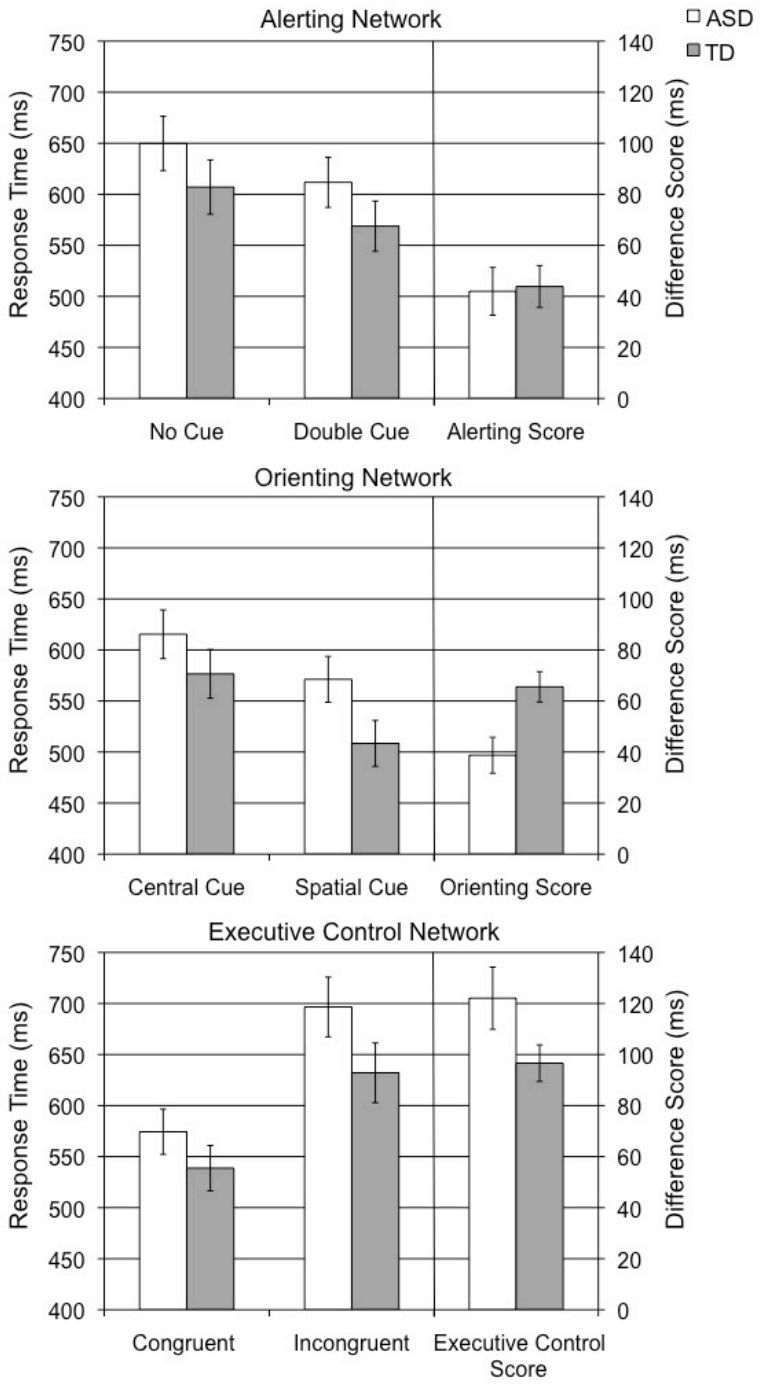

Figure 3.3. Attention network scores (right axis) and collapsed median response time for relevant cue or flanker conditions (left axis). Error bars represent one standard error of the mean.

Key Points:

- Individuals with autism spectrum disorder (ASD) exhibit widespread attentional impairments
- We investigated the efficiency of the alerting, orienting, and executive control networks in ASD and found that children with ASD demonstrate a more inefficient orienting network.
- Unlike typically developing children, children with ASD evidenced significant interdependence between alerting and executive control networks suggesting diminished executive modulation of arousal
- Additionally, increased inefficiency of the alerting network was related to greater social impairment in children with ASD.
- Domain-general impairment in modulating alertness in children with ASD was related to domain-specific clinical impairments in reciprocal social interaction.

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CHAPTER 4

Functional Brain Organization for Visual Search in Autism Spectrum Disorder

Abstract

Although previous studies have shown that individuals with autism spectrum disorder (ASD) excel at visual search, underlying neural mechanisms remain unknown. This study investigated the neurofunctional correlates of visual search in children with ASD and matched typically developing (TD) children, using an event-related functional magnetic resonance imaging design. We used a visual search paradigm, manipulating search difficulty by varying set size (6, 12, or 24 items), distractor composition (heterogeneous or homogeneous) and target presence to identify brain regions associated with efficient and inefficient search. While the ASD group did not evidence accelerated response time (RT) compared to the TD group, they did demonstrate increased search efficiency, as measured by RT by set size slopes. Activation patterns also showed differences between ASD group, which recruited a network including frontal, parietal, and occipital cortices, and the TD group, which showed less extensive activation mostly limited to occipito-temporal regions. Direct comparisons (for both homogeneous and heterogeneous search conditions) revealed greater activation in occipital and frontoparietal regions in ASD than in TD participants. These results suggest that accelerated performance in ASD may be related to enhanced discrimination (reflected in occipital activation) and increased top-down modulation of visual attention (associated with frontoparietal activation).

Individuals diagnosed with autism spectrum disorder (ASD) exhibit elementary abnormalities of attention and perception (see Dakin & Frith, 2005, for review). Atypical visuospatial processes often manifest as areas of strength and include superior performance on the Embedded Figures Test (EFT; Jarrold et al., 2005; Jolliffe & Baron-Cohen, 1997; Morgan et al., 2003; Shah & Frith, 1983), the Wechsler block design (Caron et al., 2006; Shah & Frith, 1993), and visual search tasks (O'Riordan, 2004; O'Riordan et al., 2001; Plaisted et al., 1998). Although previous studies have shown that individuals with autism excel at visual search, the brain bases for the advantage seen in ASD remain unknown. Understanding the neural mechanisms of processing strengths, such as visual search, may provide a window onto atypical profiles of sensory and cognitive processing and thus help elucidate the primary disturbances of functional brain organization in individuals with autism.

Visual search paradigms require participants to determine the presence or absence of a target item located within an array of distractors. Visual attention is guided within the array by bottom-up and top-down mechanisms (see Wolfe et al., 1994, for discussion). Bottom-up modulation of visual attention is dependent on the physical characteristics of the stimuli; the level of bottom-up stimulation is determined by differences between physical properties of the target and surrounding distractors. In contrast, top-down processes modulate bottom-up signals based on task objectives and the goals of the participant. Search difficulty is dependent on factors such as the number of items within the array (set size) and target-distractor or distractor-distractor similarity. Search efficiency is measured as the slope (ms/item) of the response time (RT) by set size function. Efficient search is represented by a relatively flat RT by set size slope (<10ms/item), and indicates that all items within the array are processed in parallel. Conversely, steeper slopes are indicative of more inefficient search processes, which require serial scanning of individual items. As similarity between distractor types increases (or if distractors are homogeneous), search for the target becomes less

dependent on set size, and proceeds in an efficient, parallel fashion. Alternatively, as similarity between target and distractors increases the saliency of the target decreases, augmenting the difficulty of search as set size increases and resulting in inefficient, serial search (Duncan & Humphreys, 1989).

Visual search relies on a network of brain areas that orient visual attention, filter irrelevant distractors, plan and execute eye-movements, and identify objects at the locus of attention. Functional neuroimaging studies of adults have revealed a widespread system of cortical and subcortical structures necessary for visual search (see Kastner & Ungerleider, 2000, for review). While bottom-up, sensory-driven mechanisms of visual attention are mediated by visual cortices, top-down guidance relies on a frontoparietal network (Corbetta & Shulman, 2002). The posterior parietal lobe is in part responsible for representing and selecting spatial locations required for visual search (Donner et al., 2000; Gitelman et al., 2002; Leonards et al., 2000; Muller et al., 2003; Nobre et al., 2003; Wilkinson et al., 2002), whereas attentional guidance and target selection are modulated by the frontal eyes fields (FEF; Muggleton et al., 2003). Additionally, the prefrontal cortex may also play a role in difficult (i.e. inefficient) searches (Anderson et al., 2007). While this role remains to be fully characterized, Anderson and colleagues hypothesize that it may relate to controlling working memory necessary for selective attention.

Though the neural correlates of visual search processes are well understood in the adult brain, the corresponding developmental literature remains very limited. Booth and colleagues (2003) found similar patterns of frontal and parietal activation between children 9 to 12 year olds and adults on a color-form conjunction visual search task. A recent cross-sectional study of individuals from eight to twenty years of age found that right hemisphere dominance for visual search increased with age in frontal and parietal regions (Everts et al., 2008). Thus, a network of frontal and parietal regions is recruited during visual attention tasks

in children and adults, though the developmental changes associated with this network are not well defined.

Studies investigating visual search in ASD have revealed consistently accelerated RTs compared to typically developing (TD) individuals, with the largest RT advantage occurring for target absent trials and trials with larger set sizes. While the greatest ASD advantage often occurs in the hardest search trials, the absence of group differences in RT on target present trials and smaller set sizes may be due to ceiling effects, as increasing difficulty of feature search (i.e., when target and distractors differ with respect to only one stimulus feature, such as orientation) has yielded more robust group differences. O'Riordan and colleagues (2001) examined visual search abilities in children with ASD using both easy (efficient) and hard (inefficient) feature search conditions, in which participants searched for either a tilted line in an array of vertical distractors (easy condition) or a vertical line among tilted distractors (hard condition). While there was no difference between TD and ASD children on the easy search task, the ASD group was significantly faster than the TD group in the hard condition. Furthermore, the ASD group evidenced shallower RT by set size slopes compared to the TD group for both conditions, indicating the cost of additional distractors was greater in TD as compared to ASD participants. The authors hypothesized that accelerated RT and reduced slope by individuals with ASD may be the result of enhanced discrimination of stimulus items and/or superior top-down modulation of excitatory and inhibitory mechanisms.

To determine if superior ASD visual search abilities are derived from enhanced discrimination, O'Riordan and Plaisted (2001) used a color-form conjunctive search task, in which the target shares a feature with each set of distractors (e.g. target was red "F" and distractors were red "E" and green "F"), to examine the effect of target-distractor similarity on RT. While increasing target-distractor similarity resulted in longer RTs for both ASD and TD

participants, the TD group was slowed to a greater extent than the ASD group, which suggests that search advantage in autism is related to enhanced visual discrimination.

To assess whether enhanced discrimination was due to superior top-down modulation of visual attention, O'Riordan (2000) examined whether individuals with ASD achieve their advantage via enhanced distractor inhibition and/or target excitation. Using a color-form conjunction the authors varied either the identity of the target (excitation of target features) or distractors (inhibition of distractor features) to examine the degree to which excitation and inhibition of object features facilitates search. While previous findings of accelerated search were replicated, the magnitude of object-based positive and negative priming effects was equivalent for both groups, suggesting that accelerated RT for individuals with ASD was not the result of greater top-down modulation of object-based representations. However, it remains undetermined whether enhanced discrimination in ASD is achieved via augmented modulation of bottom-up, lower-level perceptual processing.

Although the current study is the first fMRI investigation of visual search in ASD, previous studies have examined neurofunctional differences associated with EFT performance (Lee et al., 2007; Manjaly et al., 2007; Ring et al., 1999). On this task, TD individuals recruited a network of frontal (Lee et al., 2007; Ring et al., 1999) and parietal (Lee et al., 2007; Manjaly et al., 2007; Ring et al., 1999) regions. In contrast, individuals with ASD showed patterns of activation restricted to more posterior areas in right occipital and left superior parietal lobe (Lee et al., 2007; Ring et al., 1999), and bilateral occipital cortex and cerebellum (Manjaly et al., 2007). These results suggest that superior EFT performance by individuals with ASD may be the result of enhanced lower-level perceptual processes.

The present study investigated the neurofunctional correlates of visual search in children and adolescents with ASD and a TD comparison group using an event-related fMRI design. Specifically, we manipulated distractor-distractor similarity in a feature visual search

task to examine the differences in efficient (homogeneous distractors) and inefficient (heterogeneous distractors) search processes. Attentional modulation in homogeneous distractor composition trials should be efficient as saliency of the target is increased when surrounding distractors are in the same orientation. Alternatively, heterogeneous distractor composition should be associated with inefficient, serial search, as distractors of different orientation reduce target salience. Based on previous behavioral and fMRI studies examining visual attention, we hypothesized that performance (accuracy, RT) would be superior in ASD as compared to TD participants and that this group difference would be more pronounced for heterogeneous than for homogenous distractor composition. We further expected neurofunctional differences, with greater activity in ASD as compared to TD children in posterior occipito-temporo-parietal regions, to be interpreted as enhanced bottom-up processing. A further open question was whether performance in ASD would be primarily bottom-up, i.e., whether activity in frontal regions would be reduced in comparison with TD children.

Methods

Participants

Nine right-handed children and adolescents with ASD (all males), all of whom met DSM-IV-TR (APA, 2000) criteria for autism spectrum disorder, and an age-, nonverbal IQ-, and handedness- matched comparison group of 13 right-handed typically developing (TD) children and adolescents (all males) were included in the present study. The final ASD sample of nine was obtained from an initial sample of 13; four children with ASD were excluded from the final sample due to excessive movement during fMRI scanning. Clinical diagnoses were confirmed using the Autism Diagnostic Interview – Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), module 3 of the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), and expert clinical judgment (author AJL and

Dr. Natacha Akshoomoff). According to their ADOS scores, 7 children met criteria for a diagnostic classification of autism, one met criteria for a less severe classification of autism spectrum disorder, and one met ADOS criteria for autism in the social domain, but was below threshold in the communication domain. The latter child met full criteria for autism on the ADI-R, and was therefore included in the sample. Children with autism-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis) were excluded.

Participants in the TD group had no reported personal or family history of autism and were confirmed via parent report to be free of autism-related symptoms or any other neurological or psychiatric conditions. Independent-samples *t*-tests confirmed that the final ASD ($n = 9$) and TD ($n = 13$) groups were matched on age, $t(20) = 0.1$, $p = .93$ and nonverbal IQ, $t(17) = -0.2$, $p = .83$, as determined using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999; see Table 1). Informed consent was obtained from all participants in accordance with the University of California, San Diego and San Diego State University Institutional Review Boards.

[TABLE 4.1]

Experimental Task

The target was an upright letter "T" and distractors were Ts rotated in three cardinal orientations (90º, 180º, 270º). Each target or distractor subtended a visual angle of .35º to .38º in both dimensions, depending on orientation. In the homogeneous condition, all distractors appeared in only one orientation, while in the heterogeneous condition distractors were presented in all three possible orientations (Figure 1). Visual stimuli were presented in black on a light blue background. The search arrays contained 24 possible stimulus locations. Each trial consisted of 6, 12, or 24 stimulus elements that were pseudorandomly arranged at specific array locations subtending 3.7° by 2.7°, 5.2° by 3.7°, and 9° by 4.5°, respectively for each set size. Distractors were equally distributed on each side of the array, and the target appeared

with equal probability on each side of the midline. In half of the trials, a target appeared within the search array (target present trials). In the remaining target absent trials, only distractors were presented. There were thus 12 trial types distinguished according to distractor composition, set size, and target presence. Additional baseline trials consisted of a solitary target (target present baseline) or a single distractor (target absent baseline), displayed in the center of the screen. Twenty trials of each condition were presented for a total of 280 trials. To reduce working memory demands, a target exemplar ("T") always appeared above the search array.

[FIGURE 4.1]

The experimental task was to indicate via a two-choice button box response whether the target stimulus was present or absent. A trial began with a fixation cross ("+") presented alone for 300 ms. Next, with the fixation cross removed, the search array appeared and remained on the screen for 2200 ms. Null trials, presenting a fixation cross only, were used for temporal jittering.

The experiment consisted of four runs, each with 70 search trials and 58 null trials. Within each run, trial types were presented in an optimized pseudorandom sequence created using RSFgen (AFNI; http://afni.nimh.nih.gov). Before the scanning session, a demonstration was given and practice trials were administered with corrective feedback. Participants were instructed to respond as quickly as possible without making errors.

Prior to collection of MRI data participants completed an initial visit, which included neuropsychological and diagnostic testing, collection of behavioral data for the visual search experiment, and a mock scanning session. Behavioral data were collected to ensure participants could complete the task while in the scanner and to assess differences in performance due to the scanner environment. The purpose of the mock scanning session was

to acclimate participants to the scanner environment (e.g. loud noise, enclosed space) and to practice remaining motionless.

MRI Data Acquisition

Imaging data were acquired at the Center for Functional Magnetic Resonance Imaging at the University of California, San Diego using a GE 3Tesla HD Signa Excite scanner with an 8-channel head coil. High-resolution anatomical images were acquired using a standard FSPGR T1-weighted sequence. Each of the four functional runs was 5:10 min long, containing 128 whole-brain volumes acquired in 40 interleaved slices using a single-shot, gradient-recalled, echo-planar pulse sequence (TR 2500 ms; TE 30 ms; flip angle 90°; matrix 64 × 64; slice thickness 3.2 mm; in-plane voxel size 3.4 × 3.4 mm). Participants' heads were stabilized with foam padding to reduce motion. The experiment was presented on a Pentium III 1.7 GHz/512 MB laptop PC using Presentation software (www.neurobs.com). Behavioral responses were recorded using an MRI compatible response box. Participants viewed stimuli displayed on a back-projection screen at their feet using a mirror attached to the head coil.

Data Analysis

fMRI data analysis. Data were analyzed using the Analysis of Functional Neuroimages (AFNI; Cox, 1996). For each participant, the first four volumes of each run were discarded to remove signal equilibration effects. Each volume was slice-time and motion corrected. The four runs were then concatenated to create a single time-series with 496 volumes and smoothed with a Gaussian filter (FWHM = 6 mm). Time points with excessive motion (greater than 2mm) were censored.

The hemodynamic response function for each stimulus type was estimated using a general linear model that included separate regressors to estimate the blood-oxygen-level dependent (BOLD) response at the onset of each stimulus and at each of the next 6 time-points (0 – 15 s post stimulus onset). Impulse response functions (IRFs) were estimated across time

points 2 through 4 (5 – 10 s). A multiple regression analysis was performed on the estimated IRFs and the stimulus time series. The six motion parameters corresponding to translation and rotation were used as orthogonal regressors. Activation maps were normalized into Talairach space using AFNI auto-talairach procedures and interpolated to 3 mm^3 isotropic voxels.

One-sample *t*-tests were used to assess within-group differences for homogeneous and heterogeneous trials (separately and combined); additional two-sample independent *t*-tests were used to compare groups. A minimum cluster size of 513 mm^3, a voxel connectivity distance of 5.82mm, and a single voxel threshold of $t(8) \geq 3.827$, $p < 0.005$ (ASD within-group), $t(12) \geq 3.424$, $p < 0.005$ (TD within-group), and $t(21) \geq 3.151$, $p < 0.005$ (group comparisons) was used to correct for multiple comparisons. Pair-wise comparisons were used to compare differences between homogeneous and heterogeneous trials within each group. For these comparisons, a minimum cluster size of 756 mm^3, a voxel connectivity distance of 5.82mm, and a single voxel threshold of $t(8) \geq 3.354$, $p < 0.01$ (ASD group) and $t(12) \geq 3.054$, $p < 0.01$ (TD group) was used. All cluster corrections yielded a corrected threshold of $p < 0.05$, as determined by Monte Carlo simulation (AFNI program AlphaSim; Forman et al., 1995).

Behavioral data analysis. A mixed-model ANOVA with the factors group (ASD, TD), distractor composition (homogeneous, heterogeneous), target presence (absent, present), and set size (6, 12, 24) was conducted on median RT for correct trials. The slopes and intercepts of the median RT x set size functions were calculated for target present and absent trials in both homogeneous and heterogeneous conditions. Slope is a measure of search efficiency, reflecting the RT cost of each additional distractor. Intercept of the RT x set size function is associated with non-search, perceptual components related to the task such as early visual processing (Sternberg, 1966). Data were analyzed using SPSS 14.0. Partial eta-squared

(η_p^2) is reported as a measure of effect size. Error bars in the figures represent one standard error of the mean.

Results

Behavioral Results

Behavioral response time measures were successfully collected during acquisition of fMRI data for 8 of the 9 ASD participants and 12 of the 13 TD participants; data from two participants were lost due to equipment malfunction.

Error rates. Error rates were greater in heterogeneous compared to homogeneous trials, $F(1, 18) = 36.6$, $p < .001$, $\eta_p^2 = .63$, greater in present compared to absent trials, $F(1, 18) = 22.6$, $p < .001$, $\eta_p^2 = .56$, and increased with set size, $F(2, 17) = 22.4$, $p < .001$, $\eta_p^2 = .72$. There was no difference between groups in error rate, $F(1, 18) = 2.0$, nor were there any interaction effects between group and other factors. Correlational analyses between error rates and median RTs for each condition revealed no evidence of a speed-accuracy tradeoffs for either group. Task compliance was confirmed, as mean error rates were < 24% in each participant, and thus no individuals were excluded based on error rate. See Figure 2.

[FIGURE 4.2]

Reaction time. As illustrated in Figure 3, median RT was longer in heterogeneous than homogeneous trials, $F(1, 18) = 131.7$, $p < .001$, $\eta_p^2 = .88$, longer in target absent than target present trials, $F(1, 18) = 90.4$, $p < .001$, $\eta_p^2 = .83$, and increased as a function of set size, $F(2, 17) = 67.6$, $p < .001$, $\eta_p^2 = .88$. There was no main effect of group, $F(1, 18) = 0.0$, but there was a marginally significant group x distractor composition interaction, $F(1, 18) = 3.7$, $p < .07$, $\eta_p^2 = .17$, as individuals with ASD were slower than TD individuals in the homogeneous condition but faster in the heterogeneous condition compared to TD individuals. However, follow-up ANOVAs performed separately for homogeneous and heterogeneous trials revealed no significant group differences (Fs < 1). Separate ANOVAs performed on each group

showed a significant main effect of distractor composition for the TD comparison group, $F(1, 11) = 77.9$, $p < .001$, $\eta_p^2 = .88$, and the ASD group, $F(1, 7) = 123.4$, $p < .001$, $\eta_p^2 = .95$. In addition, there was a significant group x set size interaction, $F(1, 18) = 3.4$, $p < .03$, $\eta_p^2 = .34$, as individuals with ASD were less affected by larger set size compared to TD individuals. A separate ANOVA was used to compare baseline trials. Whereas there was no group difference in baseline target absent trials, $F(1, 18) = 1.3$, $p > .3$, $\eta_p^2 = .07$, TD individuals demonstrated significantly faster RT than individuals with ASD in the baseline target present trials, $F(1, 18) = 5.2$, $p < .04$, $\eta_p^2 = .22$.

[FIGURE 4.3]

Slopes and intercepts of the RT x set size functions for the target-present and target-absent trials from the homogeneous and heterogeneous conditions were extracted from the median RT data reported above. Slopes were steeper, $F(1, 18) = 10.9$, $p < .005$, $\eta_p^2 = .38$, and intercepts were higher, $F(1, 18) = 39.9$, $p < .001$, $\eta_p^2 = .69$, for heterogeneous than homogeneous trials. Slopes, $F(1, 18) = 16.2$, $p < .001$, $\eta_p^2 = .47$, and intercepts, $F(1, 18) = 36.3$, $p < .001$, $\eta_p^2 = .67$, were also greater in target absent as compared to target present trials. As illustrated in Figure 4, between-group analysis of RT x set size slope revealed a marginally significant effect of group, $F(1, 18) = 3.8$, $p < .07$, $\eta_p^2 = .17$. Separate ANOVAs performed on each group showed a significant main effect of distractor composition, $F(1, 11) = 16.0$, $p < .005$, $\eta_p^2 = .59$, for the TD comparison group, but no main effect for distractor composition, $F(1, 7) = 1.1$, $p > .3$, $\eta_p^2 = .14$, for the ASD group. There was no difference between groups (ASD: 1018; TD: 955) for intercepts, $F(1, 18) = 1.1$, nor were there any interaction effects between group and other factors.

[FIGURE 4.4]

fMRI Results

Presentation of activation effects will be primarily limited to two comparisons: baseline trials versus fixation and search trials versus baseline. In many cases, results for the latter comparison did not differ substantially from those for the comparison of search trials versus fixation. However, since significant group differences in RT to baseline target present trials were observed, we also present findings for the comparison of search versus fixation whenever corresponding effects were not detected for the comparison with baseline trials.

Baseline trials versus fixation. Table 2 summarizes cluster corrected regions that showed significant BOLD activity for baseline target absent and present trials compared to fixation. For clusters with volume >5000 µl, subregions are listed as the percentage of total cluster volume. Subregions are contiguous areas of cluster activation that extend beyond the peak activation (Eickoff et al., 2007). TD individuals showed a large cluster of activation, with peak in right middle occipital gyrus, and extending dorsally into inferior and superior parietal lobe. ASD participants showed no significant activation for baseline versus fixation comparisons. Activation in left primary motor cortex was seen in both groups, but did not survive cluster correction. Direct group comparison revealed greater activation in ASD than TD group in right inferior frontal gyrus.

[TABLE 4.2]

All search trials (homogeneous and heterogeneous). Figure 5a depicts cluster corrected regions that showed significant BOLD activity for all search trials (homogeneous and heterogeneous combined) compared to baseline trials (listed in Table 3). The TD group showed a large occipital activation cluster, which extended anteriorly into the fusiform gyrus. In the ASD group, similar regions of the occipital lobe were activated, with peaks in the middle occipital gyri; however, activation extended dorsally to the right inferior and bilateral superior parietal lobes. In addition, the ASD group recruited frontal cortex within the right inferior and middle frontal gyri. Direct group comparisons of all search trials versus baseline

revealed significantly greater activation for the ASD group in frontal regions including the right inferior frontal gyrus. The ASD group also showed greater activation in the superior parietal lobe, as well as in a large cluster with peak in the right middle occipital gyrus that extended into the inferior parietal lobe. For the comparison of search trials with fixation, there was greater activation of the right superior frontal gyrus (x = 20, y = -5, z = 51; *t* = 4.2) in the ASD as compared to the TD group. No inverse effects of greater activity in the TD group were detected.

[TABLE 4.3]

[FIGURE 4.5]

Homogeneous search trials. Figure 5b depicts cluster corrected regions that showed significant BOLD activity for homogeneous search trials compared to baseline (listed in Table 4). A large cluster of significant BOLD activity for the TD group was located in occipitotemporal cortex, with a peak located in the middle occipital gyrus. The ASD group showed a more distributed pattern of activation, with significant clusters appearing in right inferior gyrus, left inferior and superior parietal lobe, and bilateral occipital cortex. The ASD group also displayed activation in the supplementary motor area bilaterally, extending into the left superior frontal gyrus. A direct group comparison revealed significantly greater frontal activation for the ASD group, including the left superior frontal and right inferior frontal gyri. Additionally, the ASD group showed greater activation than the TD group in bilateral supplementary motor cortices and inferior parietal lobule, and right middle occipital gyrus. For the comparison of homogeneous search trials with fixation, greater activation in the ASD as compared to the TD group was also found in right superior frontal gyrus (x = 23, y = 2, z = 60; *t* = 4.5) . No inverse effects of greater activity in the TD group were detected.

[TABLE 4.4]

Heterogeneous search trials. Figure 5c depicts cluster corrected regions that showed significant BOLD activity for heterogeneous search trials compared to baseline (listed in Table 5). Peak activation for TD participants was located in left occipital cortex, with a cluster extending bilaterally in the occipital lobe and into the right fusiform gyrus, and right superior occipital and inferior frontal gyri. Peak activation for the ASD group was located in the right superior parietal lobe and right middle occipital gyrus. Direct group comparisons for heterogeneous versus baseline revealed no significant effects. However, group comparison for heterogeneous search versus fixation revealed greater activation for the ASD group in right superior (x = 20, y = -8, z = 51; t = 4.0) and inferior (x = 44, y = 2, z = 15; t = 4.4) frontal gyri, middle temporal gyrus (x = 47, y = -47, z = -1; t = 4.0), and areas of the occipital lobe (x = 32, y = -68, z = 33; t = 4.1). No inverse effects of greater activity in the TD group were detected.

[TABLE 4.5]

Heterogeneous versus homogeneous trials. Pair-wise comparisons were conducted for each group to examine the differences between homogeneous and heterogeneous search trials (Table 6). Greater activation for homogeneous compared to heterogeneous trials in TD participants was observed in the right temporal pole and the left postcentral gyrus, extending into the inferior parietal lobule. Inverse effects (activation greater in heterogeneous compared to homogeneous trials) in TD individuals were detected in bilateral occipital lobe and right supplementary motor area, extending into the cingulate gyrus. Pair-wise comparisons for individuals with ASD revealed no significant differences between the two conditions.

[TABLE 4.6]

Correlations with performance and diagnostic measures. These exploratory analyses were performed to examine whether brain activation was related to behavioral measures. Regions of interest (ROI) were created from clusters of activation from all trials versus baseline for all participants, and included right inferior frontal gyrus (rIFG), right

posterior parietal cortex, and left and right middle occipital gyri. Average z-scores for each ROI were computed for comparisons of homogeneous versus baseline trials and heterogeneous versus baseline trials, and then correlated with median RT, slope, y-intercept, and error rates. The RT slope for heterogeneous target present trials was significantly correlated with average z-score of the rIFG ROI in the ASD group, $r(7) = -.71$, $p < .05$, but not the TD group, $r(11) = -.03$, $p > .9$, suggesting that increased search efficiency was associated with greater inferior frontal activation in the ASD (but not the TD) group. Error rates for homogeneous trials were negatively correlated with rIFG ROI average z-score for homogeneous trials in the ASD group, $r(7) = -.72$, $p < .05$, but not the TD group, $r(11) = -.11$, $p > .7$. Conversely, error rates for heterogeneous trials were positively correlated with rIFG ROI average z-score for heterogeneous trials in the TD group, $r(11) = .73$, $p < .01$, but not the ASD group, $r(7) = -.02$, $p > .9$. All other correlations were nonsignificant, ps > .1.

Discussion

Our behavioral findings showed the expected effects of target composition, with a significantly greater number of errors and longer RTs for heterogeneous (compared to homogeneous) trials in both groups. Contrary to our expectation, we did not find a main effect of group for either error rates or RT. However, we detected a marginally significant interaction between group and search difficulty, as individuals with ASD were faster than TD individuals in the hard (heterogeneous), but slower in the easy (homogeneous) search condition. This is consistent with previous findings suggesting that individuals with ASD excel in more difficult search tasks (e.g. O'Riodan et al., 2001). Furthermore, RT by set size slopes, were significantly shallower for the ASD group, indicating that participants with ASD were affected to a lesser extent by larger set sizes. While slopes for homogeneous trials did not meet strict criteria for efficient, parallel processing (<10ms/item), they were significantly shallower compared to heterogeneous slopes in TD individuals, indicating that search

efficiency was reduced in heterogeneous compared to homogeneous search conditions. Interestingly, individuals with ASD did not demonstrate significant differences in slope for homogeneous compared to heterogeneous distractors, indicating that search efficiency was not affected by distractor composition in ASD.

The unexpected absence of a main effect of group may be explained by the marginally longer RTs on baseline target present trials in the ASD group, probably reflecting slower basic visuomotor coordination. Previous studies have shown that individuals with ASD demonstrate atypical motor preparation (Rinehart et al., 2001), but intact visual information processing (Scheuffgen et al., 2000) compared to TD individuals. This suggests that slowed visuomotor coordination may account for the unexpectedly longer RTs in the ASD group for efficient search (homogeneous distractors), whereas enhanced visual search abilities may offset slowed visuomotor coordination on the more demanding inefficient search conditions (heterogeneous distractors).

Patterns of brain activation responsible for both efficient and inefficient visual search differed between ASD and TD groups. In the TD group, activation for all search trials (homogeneous and heterogeneous combined) was found in a large contiguous cluster in posterior regions, peaking in occipital cortex and extending into the inferior temporal lobe. In the ASD group, a more distributed network of brain areas was activated, which extended beyond bilateral occipital cortex into more dorsal regions, such as the precuneus and superior parietal lobe, and also included right frontal cortices. Similar overall patterns of within-group activation effects were found when efficient and inefficient (homogeneous, heterogeneous) search trials were examined separately, with activity in frontal-parietal regions in the ASD, but not the TD group. Pair-wise comparisons revealed differences in activation for homogeneous versus heterogeneous search trials in the TD group, but not in the ASD group. Specifically, TD individuals recruited bilateral occipital and right frontal areas to a greater extent in

heterogeneous versus homogeneous trials. Absence of differences in the ASD group, along with similar slopes for both homogeneous and heterogeneous conditions suggests that behavioral performance and neural recruitment were similar for both efficient and inefficient search tasks in ASD participants.

Direct group comparisons of homogeneous and heterogeneous trials (both separately and combined) support the finding of overall more extensive activation in the ASD group. Consistent with our initial hypothesis, activation in the ASD group was significantly greater in occipito-temporal regions. However unexpectedly, the ASD also showed greater activation in frontal and parietal regions.

In agreement with previous reports investigating visuospatial strengths (Lee et al., 2007; Manjaly et al., 2007; Ring et al., 1999), we found that individuals with ASD display increased activation of occipital regions. These findings are consistent with the hypothesis that superior visual search abilities in individuals with ASD are the result of enhanced discrimination. As predicted by Caron and colleagues (2006) enhanced activation of early visual areas, as evidenced by our ASD group, may contribute to superior visuospatial abilities in autism. This finding is accordance with the enhanced perceptual functioning model (Mottron et al., 2006) and adds to the existing literature demonstrating atypically enhanced activation of visual cortices in ASD for other types of task, such as sentence comprehension (Kana et al., 2006), semantic decision (Gaffrey et al., 2007), and verbal working memory (Koshino et al., 2005).

Contrary to previous reports, we found that individuals with ASD evidenced *increased* frontoparietal activation compared to TD individuals. These effects were seen for both homogeneous and heterogeneous search conditions. Activated areas, which included superior and inferior parietal lobe and superior and inferior frontal gyri, form a functional network responsible for top-down biasing of visual attention (Kastner & Ungerleider, 2000).

In conflict with our original hypothesis, our findings suggest accelerated search performance by individuals with ASD may be related to increased activation in areas associated with top-down, in addition to bottom-up, control of visual attention. Moreover, correlations between inferior frontal activity and RT by set size slope for heterogeneous present trials demonstrated that increased activation of rIFG was inversely correlated with RT by set size slopes for heterogeneous (target present) trials in the ASD, but not the TD, group. This suggests that increased search efficiency in the ASD group may be related to increased top-down control modulated by inferior frontal regions.

Using repetitive transcranial magnetic stimulation, Muggleton et al (2003) found that stimulation to the FEFs impaired inefficient conjunctive search, but not efficient feature search. Greater activation in superior frontal gyrus as detected in our study (search task versus fixation comparison) was consistent with the FEF, with a peak detected within a few millimeters of activation peaks previously identified by Donner et al. (2002) and Shulman et al. (2003). Our finding of increased recruitment of FEF by ASD as compared to TD individuals suggests that the FEF may also serve to enhance search performance in individuals with ASD.

Our findings of enhanced frontoparietal activation stand in contrast to previous fMRI investigations of EFT performance in individuals with ASD. This may be attributed to differences between the EFT and the search paradigm implemented here. First, there are perceptual differences between locating a target embedded within a complex figure and locating a target within an array of separate distractors. Secondly, although both tasks require target-related search, target and distractors with our search paradigm remain constant while targets and complex figures vary with each trial in an EFT. This results in enhanced top-down modulation of target and distractor features by means of both positive and negative priming of target and distractor features.

O'Riordan (2000) reported no difference in positive and negative priming effects during visual search between ASD and TD individuals, which suggests that top-down modulation of object-based representations is at least intact in individuals with ASD. Top-down modulation of visual attention can influence stimulus processing by enhancing responses for attended stimuli, filtering irrelevant information, and increasing salience of stimulus features; it is dependent on feedback projections from frontal-parietal areas to visual cortices (Kastner & Ungerleider, 2000). While our finding of enhanced frontal recruitment during visual search in ASD may be consistent with enhanced top-down control of visual attention, it is surprising given previous theories of reduced prefrontal control in autism (Minshew et al., 2002). It also raises new questions regarding a model of generally reduced long distance connectivity in ASD (Just et al., 2004). Although our study did not include analyses of functional connectivity, combined participation of frontal and occipital regions during visual search suggests that cooperation between distal regions may be task-dependent, rather than generally deficient in ASD. Functional connectivity between primary visual cortex and inferior frontal cortex has been found to be reduced in autism during visuomotor coordination in the absence of a search task (Villalobos et al., 2005), whereas the present findings suggest that during visual search, prefrontal cortex including inferior frontal lobe may play an unusually enhanced role in facilitating efficient visual search in individuals with ASD.

The interpretation of our current results remains limited given a sample size that was reduced by severe motion in several children with ASD. In addition, we did not observe accelerated RT in the ASD group, similar to previous fMRI reports investigating visuospatial tasks (Lee et al., 2003; Ring et al., 1999). Such null findings may be related to the unique testing environment or relatively small samples included in functional imaging studies.

While our findings should be interpreted with some caution due to our small sample, they suggest a differential pattern of activation in individuals with ASD as compared to TD

individuals. In particular, children with ASD recruit a network including frontal, parietal, and occipital cortices, whereas activation in a matched TD comparison group was less extensive and primarily limited to occipito-temporal regions. In agreement with the hypothesis that enhanced discrimination underlies superior visual search abilities in ASD we found increased occipital activation in ASD compared to TD individuals. Additionally, our results suggest that accelerated performance in individuals with ASD, particularly increased search efficiency, may be related to enhanced top-down modulation of visual attention.

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Table 4.1. Participant characteristics.

		Autism (n = 9) M (SD) Range	Comparison (n = 13) M (SD) Range
Age		15;1 (2;6) 10;10 – 17;11	14;11 (2;11) 8;2 – 19;1
Verbal IQ		109 (15) 79 – 128	116 (10) 103 – 133
Nonverbal IQ		110 (20) 70 - 140	112 (11) 99 – 129
ADOS Algorithm Score	Communication	4 (1) 2-6	
	Social Interaction	8 (3) 4-13	
	Repetitive Behavior	0 (1) 0-2	
ADI Algorithm Score	Communication	19 (1) 18-20	
	Social Interaction	23 (3) 19-26	
	Repetitive Behavior	7 (3) 3-9	

Table 4.2. fMRI BOLD activation for baseline trials versus fixation.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (μl)	T-score
			x	y	z		
TD	Middle occipital gyrus	R	29	77	30	6129	5.6
	Angular gyurs (25.2)						
	Inferior parietal lobe (24.1)						
	Middle occipital gyrus (22.1)						
	Superior occipital gyrus (11.8)						
	Superior parietal lobe (9.2)						
	Cerebellum	R	26	-47	-25	2646	5.3
ASD > TD	Inferior frontal gyrus	R	56	26	-1	783	4.9

Table 4.3. fMRI BOLD activation for homogeneous and heterogeneous trials versus baseline trials.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (µl)	T-score
			x	y	z		
TD	Middle occipital gyrus	R	26	-80	6	37935	10.5
	R. Middle occipital gyrus (7.5)						
	R. Fusiform gyrus (7.4)						
	R. Lingual gyrus (6.7)						
	L. Fusiform gyrus (6.4)						
	L. Middle occipital gyrus (6.2)						
	L. Lingual gyrus (5.5)						
	R. Calcarine Fissure (5.4)						
	Thalamus	R	17	-29	-1	594	4.7
ASD	Middle occipital gyrus	R	35	73	14	21546	12.7
	Middle occipital gyrus (24.7)						
	Superior occipital gyrus (14.4)						
	Superior parietal lobe (10.3)						
	Angular gyrus (10.0)						
	Calcarine fissure (8.3)						
	Inferior parietal lobe (7.6)						
	Middle occipital gyrus	L	-26	77	14	15660	11.7
	Middle occipital gyrus (29.8)						
	Superior parietal lobe (16.0)						
	Superior occipital gyrus (10.2)						
	Calcarine fissure (9.3)						
	Fusiform gyrus (6.6)						
	Inferior occipital gyrus (5.1)						
	Insula	R	35	14	12	5400	9.7
	Insula (25.6)						
	Inferior frontal gyrus (24.7)						
	Precentral gyrus (9.7)						
	Middle frontal gyrus	R	8	2	57	4995	8.3
	Thalamus	L	-23	-29	3	3537	11.8
	Caudate nucleus	R	20	-8	24	2592	6.9
	Caudate nucleus	L	-20	-29	18	2241	6.9
	Precentral gyrus	R	35	-11	51	1863	7.6
	Cerebelllar vermis	R	5	-65	-10	1026	8.4
	Postcentral gyrus	L	-38	-32	54	567	5.4

Table 4.3. fMRI BOLD activation for homogeneous and heterogeneous trials versus baseline trials, Continued.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (µl)	T-score
			x	y	z		
ASD > TD	Middle occipital gyrus	R	35	-68	33	8242	5.1
	Angular gyrus (30.1)						
	Inferior parietal lobe (27.6)						
	Supramarginal gyrus (22.8)						
	Middle occipital gyrus (7.7)						
	Precuneus	R	8	-44	54	3753	4.5
	Supplementary Motor Area	L	-11	-23	48	1890	3.9
	Inferior frontal gyrus	R	35	16	9	1080	4.7
	Superior parietal lobe	L	-32	-65	48	945	4.5
	Inferior frontal gyrus	R	50	2	24	864	4.6
	Supplementary Motor Area	L	-8	-11	60	864	4.9
	Precentral gyrus	L	-47	-5	33	810	4.5
	Inferior frontal gyrus	R	50	20	21	594	4.2
	Middle occipital gyrus	R	44	-77	18	513	5.5

Table 4.4. fMRI BOLD activation for homogeneous trials versus baseline trials.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (µl)	T-score
			x	y	z		
TD	Middle occipital gyrus	R	26	-80	6	15579	8.8
	Middle occipital gyrus (20.2)						
	Fusiform gyrus (15.7)						
	Inferior temporal gyrus (11.4)						
	Inferior occipital gyrus (10.8)						
	Cerebellum (VI) (6.8)						
	Superior occipital gyrus (6.5)						
	Cerebellum (Crus I) (5.9)						
	Middle occipital gyrus	L	-29	-77	9	8937	8.8
	Middle occipital gyrus (22.5)						
	Fusiform gyrus (21.1)						
	Inferior occipital gyrus (17.9)						
	Lingual gyrus (9.2)						
	Cerebellum (Crus I) (7.7)						
	Cerebellum (VI) (6.8)						
ASD	Inferior occipital gyrus	L	-29	-68	-4	26757	11.8
	R. middle occipital gyrus (18.6)						
	L. middle occipital gyrus (18.4)						
	R. superior occipital gyrus (10.8)						
	L. superior occipital gyrus (6.0)						
	Supplementary Motor Area	L	-5	5	45	3240	7.7
	Inferior frontal gyrus	R	47	35	21	2592	6.1
	Superior parietal lobe	L	-23	-62	48	1944	8.6
	Supplementary Motor Area	L	-11	-14	57	1647	6.1
	Caudate	L	-17	2	27	1458	10.0
	Precentral gyrus	R	32	-8	48	1107	5.7
	Inferior frontal gyrus	R	44	5	24	621	4.9
	Inferior parietal lobe	L	-35	-50	36	621	6.2
	Inferior parietal lobe	L	-44	-38	42	594	4.8

Table 4.4. fMRI BOLD activation for homogeneous trials versus baseline trials, Continued.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (µl)	T-score
			x	y	z		
ASD > TD	Middle occipital gyrus	R	35	-68	33	6642	4.6
	Angular gyrus (31.7)						
	Inferior parietal lobe (28.6)						
	Supramarginal gyrus (14.8)						
	Middle occipital gyrus (10.5)						
	Precentral gyrus	R	23	-14	45	3564	4.0
	Supplementary motor area	L	-8	-14	57	3375	4.5
	Supplementary motor area	R	5	8	54	1863	3.9
	Inferior frontal gyrus	R	23	17	-13	1755	4.1
	Inferior parietal lobe	L	-41	-47	42	1620	4.2
	Superior frontal gyrus	L	-11	-2	45	1485	5.4
	Precuneus	L	-2	-47	51	1134	4.3
	Inferior frontal gyrus	R	50	35	21	891	4.2
	Inferior parietal lobe	L	-38	-59	54	648	4.1

Table 4.5. fMRI BOLD activation to heterogeneous trials versus baseline trials.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (μl)	T-score
			x	y	z		
TD	Middle occipital gyrus	L	-29	-71	-13	24408	11.6
	R. lingual gyrus (10.2)						
	L. calcarine fissure (8.5)						
	R. fusiform gyrus (8.2)						
	L. lingual gyrus (8.1)						
	R. inferior occipital gyrus (6.0)						
	L. middle occipital gyrus (5.9)						
	R. calcarine fissure (5.9)						
	Superior occipital gyrus	R	29	-71	30	783	4.6
	Inferior frontal gyrus	R	34	23	9	567	4.6
ASD	Superior parietal lobe	R	23	-68	45	2619	9.2
	Middle occipital gyrus	R	32	-86	3	513	5.9

Table 4.6. fMRI BOLD activation to homogeneous versus heterogeneous trials.

	Peak location Additional Regions (% volume of cluster)	Hemi-sphere	Talairach coordinates			Volume (µl)	T-score
			x	y	z		
TD – HOM > HET	Temporal pole	R	56	2	3	2376	5.7
	Lentiform nucleus	L	-17	-2	-7	1215	4.3
	Caudate	R	35	-14	-7	1107	4.2
	Postcentral gyrus	L	-56	-26	24	837	4.9
TD – HET > HOM	Supplementary Motor Area	R	2	11	51	1890	4.6
	Lingual gyrus	R	20	-74	-10	918	4.2
	Calcarine fissure	L	-14	-71	9	783	5.2

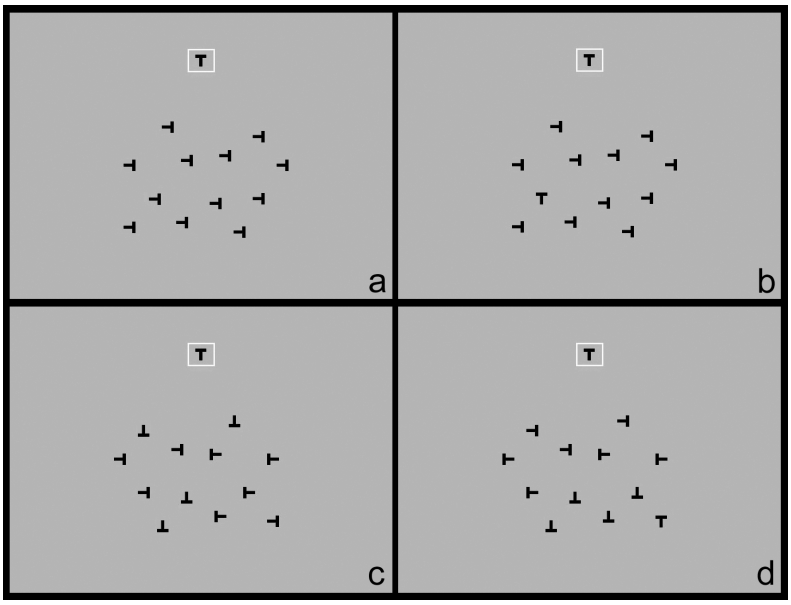

Figure 4.1. Illustration of target absent (a) and target present (b) homogeneous, and target absent (c) and target present (d) heterogeneous search trials. Light blue background is represented in gray.

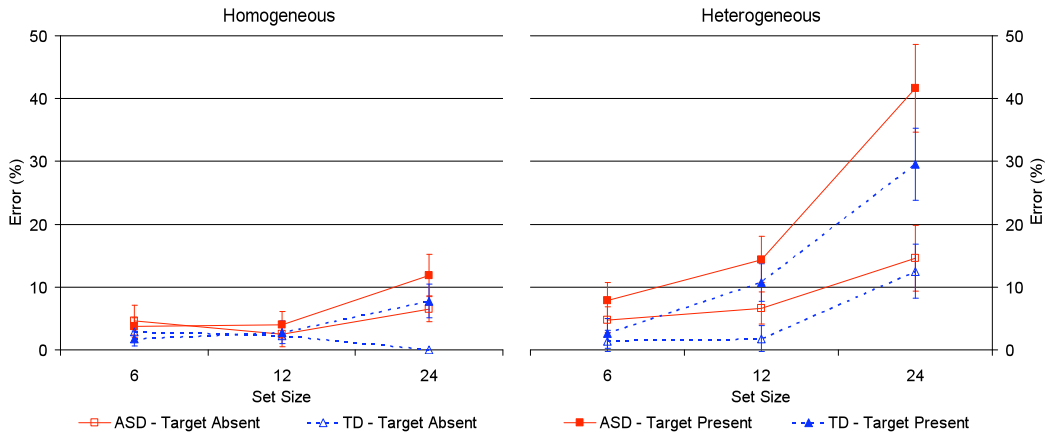

Figure 4.2. Mean error rate as a function of group, distractor composition, target presence, and set size. Error bars represent standard errors of means.

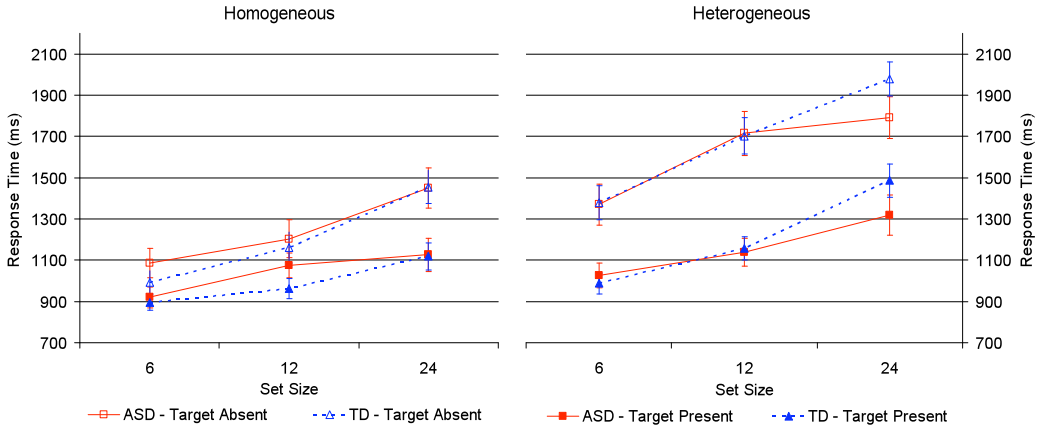

Figure 4.3. Median RT for correct trials only as a function of group, distractor composition, target presence, and set size. Error bars represent standard errors of means.

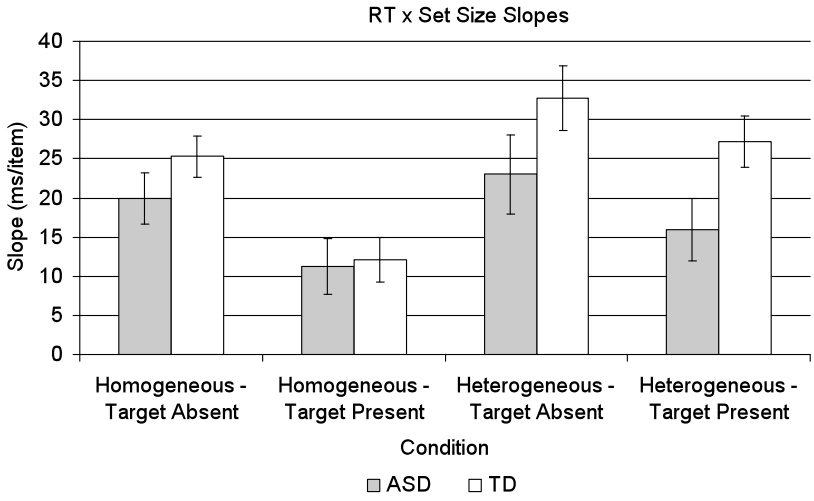

Figure 4.4. RT x set size slope for ASD and TD group as a function of distractor composition and target presence.

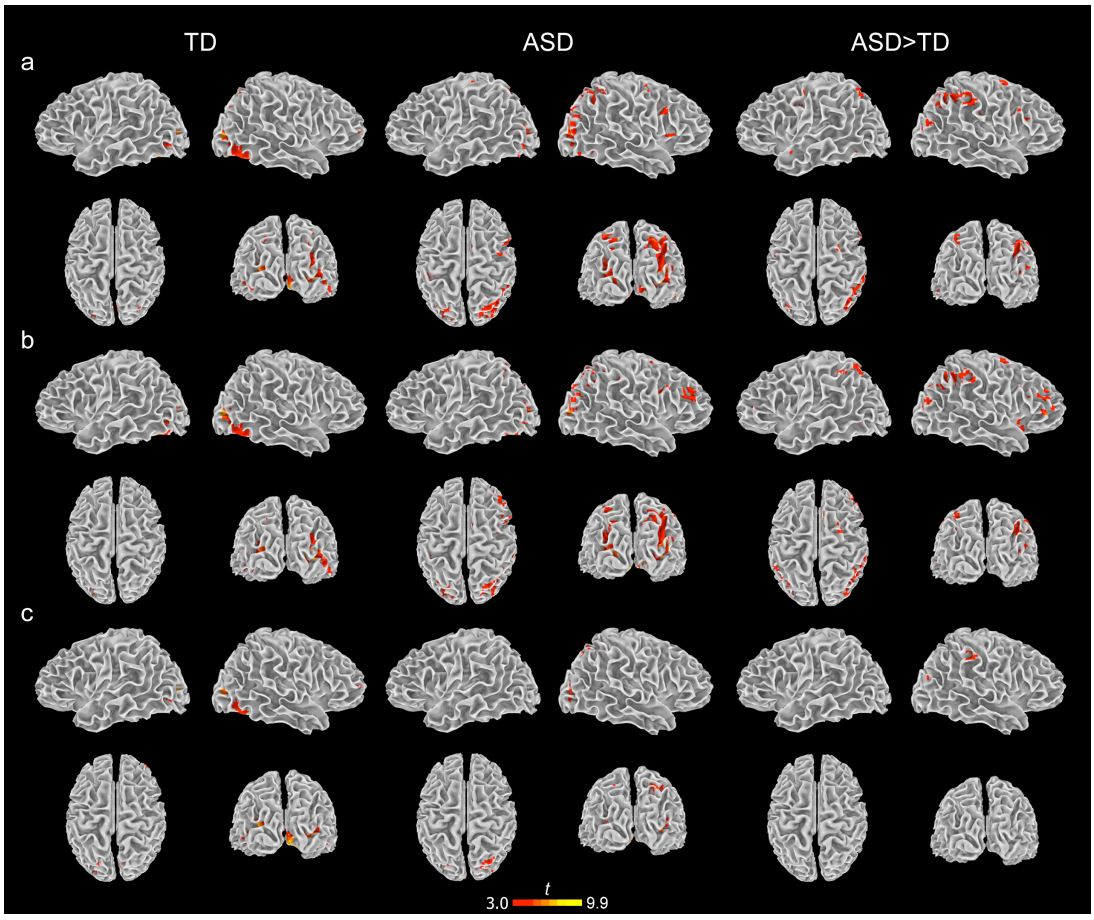

Figure 4.5. Significant activation clusters for within group comparisons and clusters showing significant effects on direct group comparisons (ASD > TD) for combined homogeneous and heterogeneous (a), homogeneous (b), and heterogeneous (c) trials.

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CHAPTER 5

Intact functional Connectivity For an "Island of Sparing" in Autism Spectrum Disorder: An fcMRI Study of Visual Search

Abstract

The present study investigated activation-based functional connectivity for a task, visual search, in which individuals with autism spectrum disorder (ASD) have demonstrated superior performance. We selected regions of interest (ROI) within two attentional networks, which have been shown to play a vital role in search, in order to examine activation and connectivity within and between attentional networks. Additionally, because prior research has demonstrated that visual search abilities in ASD may be related to degree of ASD symptomatology, we examined whether sociocommunicative impairments were related to behavioral and neural indices of search. Contrary to previous activation fcMRI studies in ASD that mostly tapped into domains of weakness and reported reduced connectivity, we found increased connectivity within and between attentional networks in ASD. Patterns of increased connectivity in ASD suggest that accelerated search abilities may be due to enhanced filtering of irrelevant information and increased coordination between attentional networks and visual-perceptual regions. In agreement with previous studies, we found that both behavioral and neural indices of search were related to the degree of sociocommunicative impairment in individuals with ASD. This association suggests that processing strengths in non-social visuo-spatial processes may be related to the development of core autistic sociocommunicative impairments.

Autism spectrum disorder (ASD) has been characterized as a disorder of abnormal neural connectivity, rather than of region-specific neural dysfunction (Belmonte et al., 2004; Rippon, Brock, Brown, & Boucher, 2007). This theoretical shift is in line with the *underconnectivity theory* of ASD put forth by Just and colleagues (2004). This theory was partially based on evidence from functional connectivity MRI (fcMRI), which is a complementary model-driven traditional fMRI activation analyses and detects interregional correlations of the blood oxygenation level dependent (BOLD) signal. Subsequent research employing different imaging modalities, including diffusion tensor imaging (DTI) and electroencephalography (EEG), has provided further evidence overall suggesting reduced structural and functional connectivity in ASD (for review, see Wass, in press).

In the fcMRI literature on ASD, two methodological approaches can be grossly distinguished: activation fcMRI, which primarily detects task-related BOLD signal fluctuations, and intrinsic fcMRI, which isolates spontaneous signal fluctuations removes through low-pass filtering (typically at 0.1Hz) and regression of modeled task effects (when non-resting data are used). Intrinsic low-frequency fluctuations may be more closely related to anatomical connectivity (Greicius, Supekar, Menon, & Dougherty, 2009; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009), whereas activation fcMRI isolates effects based on variations in behavioral performance measures and attentional focus (Prado, Carp, & Weissman, 2011; Prado & Weissman, 2011). While both approaches provide important information about interregional signal correlations, evidence of underconnectivity in ASD may depend on the methodological approach (Müller et al., in press).

One potential limitation of previous activation fcMRI studies in ASD (which include the majority of underconnectivity findings) has been the use of tasks investigating deficits associated with ASD (Thai et al., 2009). These studies have employed experimental paradigms examining domains of dysfunction in ASD, including theory of mind (Kana, Keller,

Cherkassky, Minshew, & Just, 2009; Mason, Williams, Kana, Minshew, & Just, 2008), executive function (Agam, Joseph, Barton, & Manoach, in press; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Kana, Keller, Minshew, & Just, 2007; Koshino et al., 2005; Lee et al., 2009; Solomon et al., 2009), language comprehension and production (Jones et al., 2010; Just et al., 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006), and face processing (Kleinhans et al., 2008; Koshino et al., 2008; Welchew et al., 2005). Thus, underconnectivity within the context of these studies may reflect differences in perceived task difficulty, attentional focus, or engagement, rather than reduced integrity of underlying neurocognitive networks.

Although many behavioral and clinical reports about islands of sparing and superior functioning in ASD are available, only one study to date has examined functional connectivity for a task in which individuals with ASD excel. Damarla and colleagues (in press) examined functional connectivity during an Embedded Figures Test (EFT), a task for which prior studies have demonstrated superior performance in ASD (Dakin & Frith, 2005). Findings demonstrated reduced functional connectivity in ASD, specifically between frontal and posterior (parietal, occipital) regions of interest (ROIs). However, as noted by the authors, these results need to be interpreted with caution as participants only completed twelve EFT trials (amounting to less than 2.5 minutes of fMRI data), with ASD participants responding incorrectly on approximately 25% of trials.

We examined activation-based functional connectivity for visual search – a type of task for which superior performance has been reported for ASD (Dakin & Frith, 2005). Visual search paradigms require participants to determine the presence or absence of a target item located within an array of distractor items. Distributed attentional networks are crucial for visual search, as outlined by Corbetta and colleagues (2008; 2002): a bilateral dorsal-frontal parietal network responsible for top-down, voluntary control of visual attention; and a right-

lateralized ventral frontal-parietal network associated with bottom-up modulation of attention and filtering of irrelevant information. In individuals with ASD, accelerated response time (RT) for visual search has been reported, as well as increased search efficiency (as measured by reduced RT by set size slopes), and increased perceptual encoding (as measured by RT by set size y-intercepts; Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009; O'Riordan & Plaisted, 2001; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001). We selected regions within the two attentional networks previously proposed by Corbetta and colleagues (2008; 2002) in order to examine activation and connectivity within and between attentional networks. Second, because prior research has demonstrated that visual search abilities in ASD may be associated with ASD symptomatology (Joseph et al., 2009), we also sought to examine whether sociocommunicative impairments were related to behavioral and neural indices of search.

Methods

Participants

Twenty-seven children with ASD and 24 TD children participated. After exclusion of participants with excessive head motion (see below), the final samples included 19 children and adolescents with ASD (all males; two left-handed) and 19 age-, IQ-, gender-, handedness-, and motion-matched TD children and adolescents were included in the present study (see Table 1). Clinical diagnoses were confirmed using the Autism Diagnostic Interview – Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), and expert clinical judgment according to DSM-IV criteria. Children with autism-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis) were excluded. Participants in the TD group had no reported personal or family history of autism and were confirmed via parent report to be free of autism-related symptoms or any other neurological or psychiatric conditions. Informed assent and consent

was obtained from all participants and their caregivers in accordance with the University of California, San Diego and San Diego State University Institutional Review Boards.

[TABLE 5.1]

Task procedure

The experiment was presented with a Pentium III 1.7 GHz/512 MB laptop PC using Presentation software (www.neurobs.com). Behavioral responses were recorded using an MRI compatible response box. Stimuli were projected onto a screen placed at participants' feet and were viewed using a mirror attached to the head coil.

The target was an upright "T" and distractors were Ts rotated 90º, 180º, and 270º. Target and distractors subtended a visual angle of .35º to .38º in both dimensions, depending on orientation. In the homogeneous condition, all distractors were presented in one of the three possible orientations, while in the heterogeneous condition distractors were presented in all three possible orientations. Visual stimuli were presented in black on a light blue background. The search arrays contained 24 possible stimulus locations. For each search trial, 6, 12, or 24 stimulus elements were pseudorandomly arranged at specific array locations subtending 3.7° by 2.7°, 5.2° by 3.7°, and 9° by 4.5°, respectively for each set size. Distractors were equally distributed on each side of the array, and the target appeared with equal probability on each side of the midline. The target appeared within the search array for 50% of the trials (target present); in the remaining trials, only distractors were presented (target absent). Additional baseline trials consisted of a solitary target (target present baseline) or a single distractor (target absent baseline), displayed in the center of the screen. Twenty trials of each condition (12 search, 2 baseline) were presented for a total of 280 trials. To reduce working memory demands, a target exemplar ("T") appeared above the search array.

The task was to indicate via button box response whether the target was present or absent. A trial began with a fixation cross ("+") presented alone for 300ms. Next, with the

fixation cross removed, the search array appeared and remained on the screen for 2200ms. Null trials used for temporal jittering consisted of a fixation cross presented alone for 2500ms.

The experiment consisted of four runs, each with 70 search/baseline trials and 58 null trials. Within each run, trial types were presented in an optimized pseudorandom sequence created using RSFgen (http://afni.nimh.nih.gov). Before the scanning session, a demonstration was given and practice trials were administered with corrective feedback. Participants were instructed to respond as quickly as possible without making errors.

MRI Data Acquisition

Imaging data were acquired using a GE 3Tesla HD Signa Excite scanner with an 8-channel head coil. High-resolution anatomical images were acquired using a standard FSPGR T_1-weighted sequence (TR: 11.08ms; TE: 4.3ms; flip angle: 45°; 256 × 256 matrix; 180 slices; $1mm^3$ resolution). Each of the four functional runs consisted of 128 whole-brain volumes acquired in 39/40 interleaved slices using a single-shot, gradient-recalled, echo-planar pulse sequence (TR: 2500ms; TE: 30ms; flip angle: 90°; 64 × 64 matrix; 3.2mm slice thickness; in-plane resolution $3.4mm^2$). Participants' heads were stabilized with foam padding to reduce motion.

FMRI Preprocessing

Data were analyzed using the Analysis of Functional Neuroimages suite (AFNI; Cox, 1996). For each participant, the first four volumes of each run were discarded to remove signal equilibration effects. Visual inspection and quality control (3dToutcount, 3dTqual) of each run were completed. The data were then slice-time corrected and realigned to the middle time point of the first run and co-registered to the anatomical volume using a single transformation matrix (epi_align_anat.py). Data were smoothed with a Gaussian filter to an effective full-width at half maximum of 6 mm (3dBlurFWHM), scaled to a mean of 100 (3dcalc), and concatenated (3dTcat) to create a single time-series with 496 volumes.

We adopted a method similar to previous ASD fcMRI studies in order to control for head motion (see Jones et al., 2010; Kennedy & Courchesne, 2008). First, the first temporal derivative for the six motion parameters (3 rotations, 3 translations) was calculated. Next, the magnitude of displacement was calculated as the root sum of square for each of the 496 time points. Time points with excessive head motion (>1) as well as the immediately preceding and following time points were censored from further activation and connectivity analyses. Additionally, sections of less than ten consecutive uncensored time points were excluded. Finally, the root mean square of displacement magnitudes across the entire time series was calculated as an estimate of participants' total motion. Any participant with greater than 25% of their data removed on the basis of the criteria described above was excluded from the present study (ASD = 8; TD = 5).

FMRI Activation Analysis

The hemodynamic impulse response function (IRF) for each stimulus type was estimated using a general linear model. Variable-shape IRFs for each stimulus type were estimated using piecewise linear B-spline (tent) basis functions (Saad et al., 2006). Seven tent functions were used to model the response from the onset of each stimulus type and at each of the next six time points (0 – 15s post stimulus onset). The six motion parameters corresponding to translation and rotation and a separate regressor that indicated error trials were used as orthogonal regressors. Statistical maps for each stimulus type were computed as the sum of the fit coefficients across time points 1 through 3 (2.5 – 7s), corresponding to the peak hemodynamic response. Statistical maps were interpolated to $3mm^3$ isotropic voxels and spatially normalized to the structural volume, which had been standardized to the N27 Talairach-Tournoux template using AFNI auto-talairach procedures (@auto_tlrc).

One- and two-sample *t*-tests (3dttest) were used to assess activation for homogeneous and heterogeneous trials within and between groups. All statistic maps were corrected for

multiple comparisons to a cluster corrected threshold of $p < 0.05$, using Monte Carlo simulation (AlphaSim).

Connectivity Analysis

Following high-pass filtering (125s; 3dFourier), sources of noise (linear trend, six motion parameters) were modeled and removed, using a general linear model, and residuals were used in subsequent functional connectivity analysis. Data were interpolated to $3mm^3$ isotropic voxels and spatially normalized to the structural volume, which had been standardized to N27 Talairach-Tournoux template using AFNI auto-talairach procedures (@auto_tlrc). For each participant, the mean time course for each region of interest (ROI) was extracted. The correlation between the average time course for each ROI pair was calculated and then transformed using Fisher's *r* to *z'* transformation.

Twelve functional ROIs were defined based on local maxima and minima with significant clusters of activation for all search trials for both groups combined. A sphere with a radius of 6mm was defined for each peak. These locations were chosen based on their correspondence to nodes within dosal and ventral attention networks (Corbetta et al., 2008; Corbetta & Shulman, 2002). ROIs for the dorsal network included bilateral frontal eye fields (right [rFEF]: x = 29, y = -8, z = 48; left [lFEF]: x = -23, y = -14, z = 51) and intraparietal sulci (right [rIPS]: x = 41, y = -44, z = 42; left [lIPS]: x = -26, y = -50, z = 39). For the ventral network, ROIs included right hemisphere inferior frontal gyrus (rIFG; x = 44, y = 5, z = 30), anterior insula (rINS; x = 29, y = 20, z = 9), temporal-parietal junction (rTPJ; x = 50, y = -35, z = 30), and middle frontal gyrus (rMFG; x = 35, y = 29, z = 33). Additionally, bilateral extrastriate (right [rMOG]: x = 26, y = -80, z = 12; left [lMOG]: x = -29, y = -80, z = 6) and primary visual cortex (right [rV1]: x = 17, y = -83, z = -4; left [lV1]: x = -11, y = -86, z = -1) were selected in order to examine functional connectivity between attentional networks and visual regions in the occipital lobe (See Figure 1).

[FIGURE 5.1]

Behavioral Data Analysis

Mean error rates and median RT for correct trials were entered into a 2 (group: ASD, TD) x 2 (distractor type: homogenous, heterogeneous) x 2 (target presence: absent, present) x 3 (set size: 6, 12, 24) mixed-model repeated measures ANOVA. Slopes and y-intercepts for target absent and present trials of homogenous and heterogeneous conditions were determined from the regression line associated with median RT at each set size. These values were entered into a 2 (group: ASD, TD) x 2 (distractor type: homogenous, heterogeneous) x 2 (target presence: absent, present) mixed-model repeated measures ANOVA. D-prime (d') and C-criterion (C) were calculated to assess the strength of the signal-to-noise (increased d' is associated with higher signal-to-noise) and participant response strategy (positive vs. negative C values indicate that, compared to the ideal observer, a participant shows more target absent or target present responses more than the ideal observer; positive C values indicate that a participant makes target absent responses more than the ideal observer, respectively). These values were entered into a 2 (group: ASD, TD) x 2 (distractor type: homogenous, heterogeneous) x 3 (set size: 6, 12, 24) mixed-model repeated measures ANOVA.

Results

Behavioral Results

Behavioral data were successfully collected from of 17 of 19 participants with ASD and 18 of 19 TD participants; data from the three participants were lost due to equipment malfunction.

Error rates. Mean error rates did not significantly differ between ASD (M = 13%) and TD (M = 9%) groups, $F(1, 33) = 1.9$, $p = .2$, nor were there any significant interactions between group and any other factor ($ps > .1$). Error rates were greater in heterogeneous (15%) compared to homogeneous (7%) trials, $F(1, 33) = 50.4$, $p < .01$, greater in present (14%)

compared to absent (8%) trials, $F(1, 33) = 11.2$, $p < .01$, and increased with set size (5%, 9%, and 19% for 6, 12, and 24, respectively), $F(2, 66) = 103.5$, $p < .01$. Interactions between distractor type and set size and target presence and set size were significant ($ps < .01$). Mean error rate for the baseline conditions did not differ significantly between ASD (M = 4%) and TD (M = 4%) groups, $F(1, 33) = 0.01$, $p = .8$, and was greater for absent (ASD: 5%; TD: 6%) than present (ASD: 2%; TD: 2%) trials in both groups.

Response time. There was no difference in RT between ASD (M = 1220ms) and TD (M = 1178ms) groups, $F(1, 33) = 0.6$, $p = .4$, nor were there any significant interactions between group and any other factors ($ps > .1$). As expected, RT was longer for heterogeneous (M = 1339ms) compared to homogenous conditions (M = 1058ms), $F(1, 33) = 308.6$, $p < .01$, longer for absent (M = 1362ms) compared to present (M = 1035ms) trials, $F(1, 33) = 193.5$, $p < .01$, and increased with set size (M = 1037, 1190, and 1369 ms, for 6, 12, and 24, respectively), $F(1, 33) = 197.6$, $p < .01$. Additionally, there were significant interactions between distractor type and target presence and distractor type and set size, and between target presence and set size ($ps < .01$). Baseline RT did not significantly differ between ASD (M = 788ms) and TD (M = 759ms) groups, $F(1, 33) = 0.6$, $p = .5$, and was significantly longer for target absent (ASD: 844ms; TD: 820ms) compared to target present (ASD: 732ms; TD: 698ms) trials for both groups.

Slopes and intercepts. RT × set size slopes did not differ between ASD (M = 16.7ms/item) and TD (M = 19.1ms/item) groups, $F(1, 33) = 1.0$, $p = .3$, nor were there any significant interactions between group and any other factor ($ps > .2$). Slopes were larger in heterogeneous (ASD: 19.5; TD: 23.1) compared to homogenous (ASD: 13.9; TD: 15.1), $F(1, 33) = 20.4$, $p < .01$, and larger in absent (ASD: 21.4; TD: 24.3) compared to present (ASD: 12.0; TD: 13.9) trials, $F(1, 33) = 32.4$, $p < .01$.

Y-intercepts of RT × set size functions did not differ between ASD (M = 986ms) and TD (M = 910ms) groups, $F(1, 33) = 1.9$, $p = .2$; however, there was a significant group by distractor type by target presence interaction, $F(1, 33) = 4.9$, $p < 05$. Simple effects revealed that the interaction was due to marginally increased y-intercepts for the ASD group in homogeneous present (ASD: 873.8; TD: 793.6) and heterogeneous absent (ASD: 1285.4; TD: 1130.5) conditions (*ps* < .1).

ADOS correlations. Correlational analyses between slopes and y-intercepts of RT × set size functions for homogeneous and heterogeneous target absent and present conditions revealed a significant association between homogeneous target absent slope and ADOS Communication scores, $r(16) = -.57$, $p < .05$, and Total, $r(16) = -.62$, $p < .05$, in the ASD group.

d' and C-criterion. Both d-prime and C-criterion values did not differ significantly between groups, nor were there any significant interactions with group and any other factors (*ps* > .1).

fMRI Results

Participant motion. Based on the criteria described above, the mean percentage of data censored from all included participants (ASD = 19; TD = 19) was less than 5%. Percentage of data censored and amount of total motion did not differ between groups (see Table 1). The percentage of censored time points and the amount of total motion were not significantly correlated with age and IQ for TD participants and with age, IQ, and ADOS algorithm scores for ASD participants included in the current sample (*ps* > .1). Excluded ASD participants (n = 8) did not differ from those included in the ASD group with respect to age or IQ, but did have marginally higher social and total algorithm scores on the ADOS (*ps* < .1). Excluded TD participants (n = 5) did not differ in IQ but were significantly younger than those included in the TD group ($p < .01$).

Activation results. Both groups exhibited activation in regions previously implicated in voluntary control of attention and visual search, including dorsal frontal parietal regions such as bilateral frontal eye fields and intraparietal sulci (Table 2). Both groups also showed activation of bilateral insula and right inferior and middle frontal gyri associated with the ventral attentional network. In addition, deactivation of bilateral TPJ, associated with filtering of irrelevant distractors (Shulman, Astafiev, McAvoy, d'Avossa, & Corbetta, 2007; Wei, Muller, Pollmann, & Zhou, 2009), was also present in each group. Lastly, both groups also exhibited activation of occipital cortex.

[TABLE 5.2]

[FIGURE 5.2]

Between group comparisons revealed significant differences in activation for specific trial types but not all search trials combined. Specifically, TD individuals showed significantly greater activation in the left putamen for homogeneous present trials. However, as seen in Figure 2, individuals with ASD show diffusely greater activation in many regions.

Table 3 lists regions that demonstrated significant activation for all search trials for ASD and TD groups combined. ROIs were selected from local maxima and minima within these significant clusters that corresponded to regions of dorsal and ventral attentional networks as well as regions within the occipital lobe. Separate mixed-model ANOVAs with within subjects factors distractor type (homogeneous, heterogeneous) and target presence (present, absent) and between subjects factor group (ASD, TD) were conducted on each ROI (see Table 4). There was no significant main effect of group for any ROI.

[TABLE 5.3]

[TABLE 5.4]

ADOS correlations. Correlational analyses for ROI activation to homogenous and heterogeneous trials and ADOS algorithm scores revealed significant associations between

rMFG activation and ADOS Communication scores, $r(18) = .49$, $p < .05$, for the homogeneous condition, and Communication, $r(18) = .64$, $p < .01$, and Total, $r(18) = .49$, $p < .05$, scores for the heterogeneous condition. Additionally, there were significant correlations between activation of lIPS and Social, $r(18) = -.49$, $p < .05$, and Total, $r(18) = -.56$, $p < .05$, scores for the homogeneous condition and Social, $r(18) = -.49$, $p < .05$, and Total, $r(18) = -.52$, $p < .05$, scores for the heterogeneous condition.

Connectivity results. A goal of the current study was to examine functional connectivity within and between attention networks involved in visual search and between these networks and visual-occipital regions. Within-network connectivity was examined by averaging z' scores for within-network ROI pairs. Between-network connectivity was examined by averaging z' scores for between-network ROI pairs. In addition, for between-network connectivity, mixed-model ANOVAs were used to examine inter-network connectivity of each region with dorsal and ventral networks.

Within-network connectivity. A mixed model ANOVA was used to examine within-network connectivity with within subject factor network (dorsal, ventral, visual) and between subject factor group (ASD, TD). There was a significant main effect of network, $F(2, 72) = 5.3$, $p < .05$. Simple effects revealed that dorsal network connectivity was greater than ventral, $t(37) = 5.6$, $p < .05$, but not visual, $p = .3$, networks. No other differences in within-network connectivity were found between networks. There was a marginally significant main effect of group, $F(1, 36) = 3.7$, $p = .06$, as individuals with ASD evidenced higher mean z' scores for within-network connections. The interaction between group and network was not significant, $F(3, 108) = .46$, $p = .6$.

Between-network connectivity. A mixed-model ANOVA was used to examine between-network connectivity with within subject factor inter-network connection (dorsal-ventral, dorsal-visual, ventral-visual) and between subjects factor group (ASD, TD). There

was a significant main effect of inter-network connection, $F(2, 72) = 88.2$, $p < .01$, with increased dorsal-ventral connectivity relative to both dorsal-visual, $t(37) = 9.1$, $p < .01$, and ventral-visual connectivity, $t(37) = 11.9$, $p < .01$. Additionally, there was a marginally significant main effect of group, $F(1, 36) = 3.1$, $p = .08$, with greater inter-network connectivity in ASD as compared to TD individuals (see Figure 3).

Between-network connectivity was also assessed with a series of mixed-model ANOVAs with within subjects factors consisting of two sets of network-specific ROIs; e.g. dorsal-ventral connectivity was assessed with within subjects factors dorsal (rFEF, lFEF, rIPS, lips) and ventral (rMFG, rINS, rIFG, rTPJ) and between subjects factor group (ASD, TD). For dorsal-ventral connectivity, there were significant main effects of dorsal and ventral ROIs and a significant interaction between-network connectivity (*ps* < .01). There was no significant main effect of group, $F(1, 36) = 1.7$, $p = .20$, and no significant interaction between group and dorsal regions, $F(3, 108) = 2.0$, $p = .12$; however, there was a marginally significant interaction between group and ventral regions, $F(3, 108) = 2.3$, $p = .08$. Between group comparison of average dorsal connectivity for each ventral ROI showed significantly increased functional connectivity between rTPJ and dorsal network in ASD, $t(37) = 2.3$, $p < .05$; dorsal connectivity for the other ventral ROIs were not significantly different between groups (*ps* > .3).

For dorsal-visual connectivity, there were significant main effects of dorsal and visual ROIs and a significant interaction between-network connectivity of ROIs (*ps* < .01). There was no significant main effect of group, $F(1, 36) = .83$, $p = .37$, and no significant interaction between group and visual regions, $F(3, 108) = .56$, $p = .64$; however, there was a marginally significant interaction between group and dorsal regions, $F(3, 108) = 2.6$, $p = .06$. Between group comparisons of average visual connectivity for each dorsal ROI showed marginally increased functional connectivity between rIPS and visual network in ASD, $t(37) = 1.8$, $p =$

.08; dorsal connectivity for the other visual ROIs were not significantly different between groups (*ps* > .1).

For ventral-visual connectivity, there were significant main effects of ventral and visual ROIs and a significant interaction between network connectivity of ROIs (*ps* < .05). There were no significant interactions between group and either network (*ps* > .5). However, there was a significant main effect of group, $F(1, 36) = 5.6$, $p < .05$; individuals with ASD exhibited greater functional connectivity between ventral and visual ROIs as compared to TD individuals.

[FIGURE 5.3]

ADOS correlations. No correlation between ADOS algorithm scores and mean within- and between-network connectivity reached significance (*ps* > .3).

Discussion

We investigated activation-based functional connectivity for a processing strength in ASD. Contrary to previous activation fcMRI studies in ASD that reported reduced connectivity for task domains of processing weakness, we found intact or subtly increased connectivity within and between attentional networks in ASD during visual search. However, in contrast to some previous behavioral and neuroimaging studies of visual search in ASD, we did not detect robust group difference in performance or activation. Finally, in agreement with previous studies, we found that both behavioral and neural indices of search are related to the degree of sociocommunicative impairment in individuals with ASD. Each of these findings will be discussed below.

Performance and fMRI Activation

Within and combined groups results replicated findings from prior behavioral (Duncan & Humphreys, 1989) and neuroimaging (Donner et al., 2002; Wei et al., 2009; Wilkinson, Halligan, Henson, & Dolan, 2002) studies of visual search. Both groups were

faster to respond to homogeneous compared to heterogeneous and target present compared to absent trials. Further, both groups showed activation and deactivation in expected brain regions (Donner et al., 2002; Muller et al., 2003; Wei et al., 2009).

However, no group differences were found for any behavioral search measure. This finding contradicts previous studies of visual search abilities in ASD, which have reported superior performance in ASD. Similarly, we did not find differential patterns of activation, including greater activation in posterior brain regions in ASD (Keehn, Brenner, Palmer, Lincoln, & Muller, 2008; Lee et al., 2007; Manjaly et al., 2007; Ring et al., 1999). One possible explanation for this finding is that more impaired individuals could not tolerate the scanner environment or were excluded due to movement within the scanner. Based on the correlational analyses from the current study (discussed in greater detail below) and a previous study (Joseph et al., 2009), greater sociocommunicative impairment is related to faster, more efficient visual search abilities in ASD. In the present study, individuals excluded due to motion had increased ADOS scores relative to ASD participants included in the present sample. Therefore, one possible explanation for equivalent performance between ASD and TD groups in the present study as well as previous fMRI studies investigating processing strengths (Lee et al., 2007; Ring et al., 1999) is the limited range of functioning of participants included in neuroimaging studies.

fcMRI

This study is among the first to examine activation-based functional connectivity for a processing strength in ASD. In contrast to previous studies that have used tasks tapping into domains of impairment, we found intact functional connectivity in ASD. This finding is in agreement with an often overlooked prediction in the original proposal of the underconnectivity theory by Just et al. (2004), which was considered to apply only to task domains of processing weakness. However, the underconnectivity theory also predicts that

individuals with ASD will show generally less dependence on frontal brain regions, irrespective of task domain. Our results do not support this prediction. In fact, our ASD group had equal or greater connectivity for ROI pairs that included frontal regions.

Our findings revealed intact and even marginally increased within-network connectivity in ASD. Likewise, between-network connectivity showed intact or increased connectivity across all inter-network connections in ASD. Further examination of between-network connectivity revealed significantly increased functional connectivity between rTPJ and the dorsal network in ASD. Deactivation or suppression of rTPJ during search has been taken as evidence of filtering of task-irrelevant information (Shulman et al., 2007; Wei et al., 2009). One potential source of this top-down signal that biases attention for task-relevant information and results in rTPJ suppression is the dorsal attention network (Corbetta et al., 2008). Thus, increased functional connectivity between rTPJ and dorsal network in ASD may suggest that individuals achieve their superior performance via enhanced top-down control that biases attention and results in more efficient filtering of task-irrelevant information.

In addition, individuals with ASD also showed increased connectivity between both attentional networks and occipital regions compared to TD individuals. Specifically, individuals with ASD had significantly increased rIPS-visual and ventral-visual connectivity. As discussed above, prior studies have demonstrated that individuals with ASD exhibit greater activation of visual cortex, suggesting that they may rely more on visual-perceptual processes compared to TD individuals. Visual-perceptual processes associated with activation of occipital cortex are related to both feed-forward and feed-backward mechanisms reflecting top-down and stimulus-driven processes. Our connectivity measures do not permit assumptions about directionality of information flow; however, increased functional connectivity between attentional networks and occipital ROIs suggests that superior

performance in visuo-spatial tasks may be related to communication between visual regions and attentional networks and not purely to increased activation in visual processing regions.

Methodologically, our processing pipeline was very similar to previous activation fcMRI studies. A recent survey of fcMRI studies in ASD by Müller and colleagues (2011) indicated that activation fcMRI studies, which use ROI rather than whole brain analyses and do not task-regress and low-pass filter, may be more likely to report underconnectivity in ASD. The results of the present study suggest that the type of task may play an additional important role, indicating that prior underconnectivity reports in the fcMRI literature on ASD may relate to the almost exclusive selection of tasks tapping into domains of impairment. For example, a prior intrinsic functional connectivity study demonstrated no difference for the Task-Positive Network (i.e., the dorsal network) in individuals with ASD compared to TD individuals (Kennedy & Courchesne, 2008). This finding contrasts with previous activation-based fcMRI studies in ASD, which have generally reported reduced frontal-parietal connectivity (Just et al., 2007; Kana et al., 2006). Preserved dorsal network connectivity in the present study suggests that underconnectivity between dorsal frontal-parietal regions may have resulted from task selection and task-related BOLD signal fluctuations (Jones et al., 2010), although future studies directly comparing strengths and weaknesses in a single ASD will be necessary to confirm this hypothesis.

Correlations with Autism Symptomatology

Similar to Joseph and colleagues (2009), we found that increased search efficiency is related to greater autism symptomatology. Additionally, while we did not find any association between sociocommunicative impairment and functional connectivity measures, we did find associations with the levels of activation. In agreement with Gomot and colleagues (2008), we found that increases in activation of the right middle frontal gyrus were related to greater social impairment. We also found that reduced activation of left intraparietal sulcus was

related to greater ASD symptomatology. Gomot and colleagues (2008) hypothesized that increased activation of the middle frontal gyrus and the relationship to greater social and communication difficulties may be related to over-focused attention in ASD, which could be beneficial during tasks such as visual search but have consequences for the adaptive allocation of attention during dynamic social interactions.

Prior research has suggested that the parietal lobe may be responsible for creating and maintaining a saliency map, which is used to direct visual attention (Corbetta & Shulman, 2002). Therefore the inverse relationship between activation of the left intraparietal sulcus and sociocommunicative impairment may implicate a narrower attentional focus. The relationship between over-focused attention and increased social impairment has been demonstrated elsewhere (Liss, Saulnier, Fein, & Kinsbourne, 2006) and suggests that abnormalities in domain-general attention function may be related to ASD symptomatology. While the functional and developmental significance of this brain-behavior relationship has yet to be fully understood, the association between behavioral and neural indices of search efficiency and degree of social impairment suggests that processing strengths in non-social visuo-spatial processes may be related to the development of core autistic sociocommunicative impairments.

Conclusions

Functional connectivity MRI research in diverse neurodevelopmental disorders has demonstrated that functional underconnectivity is not unique to ASD, but characteristic of multiple populations, including attention deficit hyperactivity disorder and Tourette syndrome (Uddin, Supekar, & Menon, 2011). The results of the present study demonstrate intact or increased activation-based functional connectivity in ASD for a tasks tapping into a processing strength. Prior intrinsic functional connectivity studies have found evidence of both increased and decreased functional connectivity in ASD (Müller et al., 2011). Taken together,

these and our findings suggest that brain organization ASD may not be characterized by general underconnectivity, but by atypical profiles of both decreased and increased connectivity. This differential pattern may relate to the ASD phenotype, which is characterized by a profile of both processing strengths and weaknesses.

Previous descriptions of attention in ASD have characterized individuals with the disorder as both over-focused and yet easily distracted. The results of the present study suggest that these behavioral patterns may relate to two neurofunctional anomalies. First, increased connectivity between ventral attention networks and visual-occipital areas suggest that individuals with ASD may achieve superior performance based on increased cooperation between visual-perceptual regions and attentional networks. Second, increased connectivity between dorsal attention networks and rTPJ may relate to greater ability to filter irrelevant distractors in ASD. However, it remains unclear how these two paradoxical states – over-focused and highly distractible – come to represent attention function in ASD? One hypothesis is that internal and external conditions may facilitate either an active (hyper-focused) or passive (hypo-focused) attentional state. In the hyper-focused state, volitional control of attention (dorsal network) may be engaged to a greater degree and responsible for filtering behaviorally irrelevant information; however, in the passive state, the dorsal network may not be engaged and top-down attentional control may be ungoverned. This could result in states of both over-focused attention as well as uncontrolled, highly distracted attentional states, in which top-down resources would not be allocated to reduce attention capture by behaviorally-irrelevant information (for example see Gomot et al., 2008 vs. Gomot et al., 2006).

Finally, the two attentional states may have important implications for the adaptive allocation of attention. As demonstrated by both the current and previous studies, behavioral and brain measures of search efficiency are related to increased sociocommunicative impairment. Over-focused attention, which may permit individuals with ASD to excel at

visual search, may have costly repercussions when it comes to attending to relevant information necessary to perceive subtle social cues and successfully participate in rapid, dynamic social interactions. Continued research examining processing strengths in ASD may yield an alternative and complementary understanding of deficits in social-information processing and the neuropathological processes at work in ASD.

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Table 5.1. Participant characteristics. IQ determined using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

		ASD (n = 19) M (SD) Range	TD (n = 19) M (SD) Range	t-value	p
Age (years; months)		13;10 (2;9) 8;10 – 18;4	14;0 (2;5) 9;3 – 18;6	-.17	.86
Verbal IQ		110.3 (14.0) 88 – 147	110.0 (14.0) 74 – 133	.08	.94
Nonverbal IQ		113.0 (10.2) 93 – 131	112.2 (12.3) 85 – 129	.20	.84
Full-Scale IQ		112.9 (11.8) 96 – 141	113.0 (14.0) 77 – 140	-.01	.99
Total motion		.24 (.20) .02 – .73	.19 (.14) .03 – .63	.88	.38
Percentage censored		.05 (.07) 0 – .22	.04 (.06) 0 – .22	.49	.63
ADOS Algorithm Scores	Comm-unication	3.1 (1.8) 0 – 6			
	Social Interaction	7.8 (2.4) 4 – 13			
	Repetitive Behavior	2.0 (1.4) 0 – 5	n/a	n/a	n/a

Table 5.2. fMRI BOLD activation for all search trials for ASD and TD groups.

[1]Homogeneous target present condition.

Group	Peak location	Hemi-sphere	Talairach coordinates			Volume (voxels)	T-score
			x	y	z		
ASD	Middle occipital gyrus	L	-29	-80	6	1372	9.7
	Postcentral gyrus	L	-44	-29	48	359	7.2
	Thalamus	L	-23	-26	-1	185	8.9
	Middle cingulate cortex	R	8	8	45	169	8.9
	Thalamus	R	8	-26	-4	159	8.6
	Precentral gyrus	R	38	-11	39	66	6.1
	Supramarginal gyrus	L	-59	-41	30	65	-6.8
	Thalamus	R	23	-29	3	61	8.7
	Insula	R	32	20	9	61	7.0
	Inferior frontal gyrus	R	47	8	30	55	5.1
	Inferior parietal lobe	L	-35	-77	36	52	-5.3
	Superior parietal lobe	L	-20	-62	42	40	5.7
	Insula	L	-32	17	9	38	6.0
	Putamen	R	20	11	12	35	5.5
	Rolandic operculum	R	38	-23	21	30	-5.8
	Middle temporal gyrus	R	47	-53	12	29	-5.6
	Calcarine gyrus	L	-11	-59	12	29	-6.1
	Putamen	L	-23	-2	9	22	4.8
	Caudate	R	5	2	12	16	5.6
	Middle frontal gyrus	L	-20	11	45	12	-4.6
TD	Middle occipital gyrus	L	-29	-80	9	1274	9.8
	Thalamus	L	-23	-32	12	346	8.8
	Frontal eye fields	L	-38	-17	51	279	6.9
	Supplementary motor area	L	-2	8	48	253	8.9
	Thalamus	R	23	-29	3	66	8.4
	Superior parietal lobe	L	-23	-56	45	60	6.0
	Insula	L	-29	20	9	59	6.5
	Thalamus	R	14	-17	18	59	6.7
	Insula	R	29	17	9	51	6.9
	Angular gyrus	L	-38	-74	33	39	-6.1
	Putamen	L	-29	-8	3	29	5.2
	Frontal eye fields	R	26	-5	45	25	5.1
	Angular gyrus	R	38	-74	39	19	-5.3
	Cerebellum	L	-32	-53	-22	13	6.4
TD > ASD	Putamen[1]	L	-23	-5	15	45	3.6

Table 5.3. fMRI BOLD activation for all search trials for all participants.

Peak location Additional regions (% volume of cluster)	Hemi- sphere	Talairach coordinates			Volume (voxels)	T-score
		x	y	z		
Middle occipital gyrus	L	-29	-80	6	5069	13.1
Precentral gyrus	L	-38	-17	51	750	8.9
Middle cingulate cortex	R	8	8	45	546	10.6
Inferior parietal lobe	L	-35	-77	36	502	-7.9
Frontal eye field	R	29	-8	48	309	7.0
Precuneus	L	-11	-56	15	222	-5.8
Middle temporal gyrus	R	47	-56	18	215	-6.6
Superior temporal gyrus	R	59	-35	21	77	-4.6
Precentral gyrus	L	-44	-2	33	50	7.0
Precuneus	L	-17	-56	60	39	-5.6
Middle frontal gyrus	R	35	29	33	32	4.9
Superior frontal gyrus	L	-20	14	42	29	-5.2
Inferior frontal gyrus	L	-47	29	6	26	-4.9
Superior parietal lobe	R	20	-53	63	23	-4.9
Fusiform gyrus	L	-20	-41	-13	21	-5.7
Rolandic Operculum	R	38	-23	21	21	-5.1
Middle cingulate cortex	R	17	-35	36	19	-5.6
Middle orbital gyrus	L	-35	38	-1	16	-4.9
Insula	R	38	-20	6	15	-4.5

Table 5.4. Statistical analysis of activation for regions of interest. * $p < .05$; ** $p < .01$.

		Analysis of variance results						
Brain Region		Group $F(1, 36)$	Distractor type $F(1, 36)$	Group × distractor type $F(1, 36)$	Target presence $F(1, 36)$	Group × target presence $F(1, 36)$	Distractor type × target presence $F(1, 36)$	Group × distractor type × target presence $F(1, 36)$
Dorsal network	R. FEF	.02	10.97**	.42	4.94*	2.21	9.18**	14.82**
	L. FEF	.70	.56	1.54	1.2	.19	3.71	5.04*
	R. IPS	1.15	.55	1.44	2.49	1.13	5.08*	9.04**
	L. IPS	.66	10.64**	.02	.70	.86	6.90*	5.55*
Ventral network	R. INS	.45	5.82*	.69	2.68	.07	10.24**	5.56*
	R. IFG	.40	.87	4.18*	16.32**	.01	5.46*	4.45*
	R. TPJ	.86	2.93	2.11	.82	.09	.50	5.86*
	R. MFG	.02	1.03	.10	.00	.00	.96	7.50**
Visual regions	R. MOG	.29	1.51	.08	6.47*	.41	.69	1.19
	L. MOG	1.05	12.95	.14	2.73	.00	14.11**	6.74*
	R. V1	1.46	16.73**	1.60	1.88	.11	1.20	.32
	L. V1	.36	10.34**	.41	1.13	.20	.01	3.84

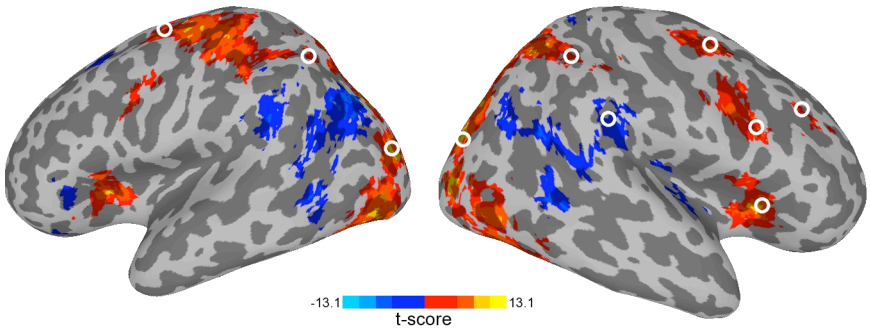

Figure 5.1. Significant activation clusters for combined group analysis for all search versus null trials. White circles represent ROIs corresponding to dorsal and ventral networks and visual-occipital regions. Note: ROIs placed in primary visual cortex are not displayed.

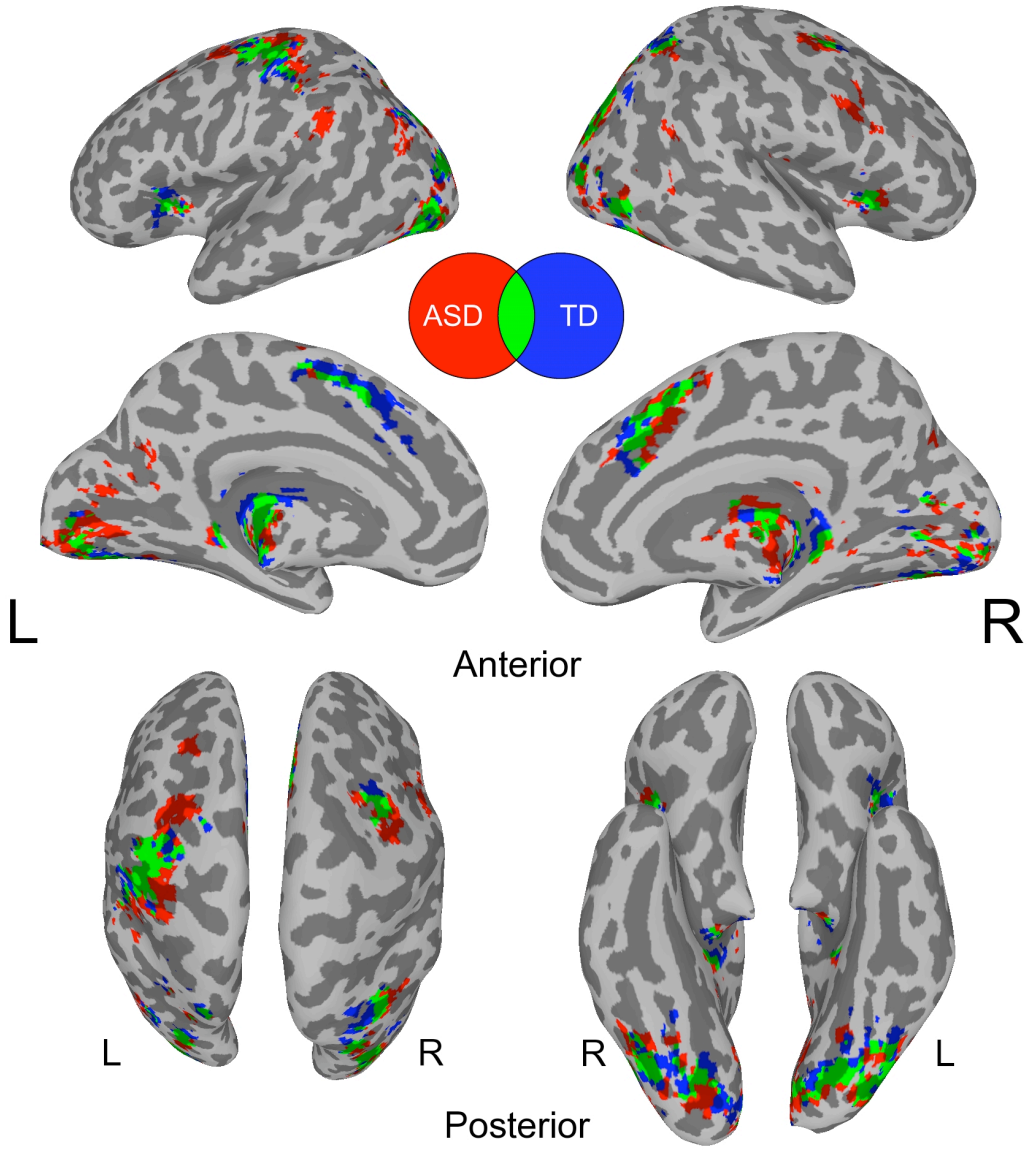

Figure 5.2. Significant activation clusters for within group comparisons for all search versus fixation trials. Significant activation in red for ASD group, blue for TD group, and green for areas of overlapping activation for both groups.

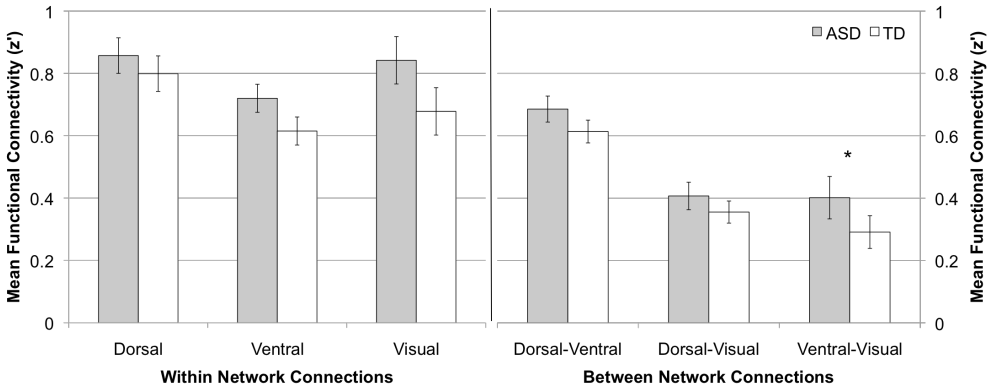

Figure 5.3. Mean z' scores for within and between-network connections. Error bars represent one standard error of the mean. * $p < .05$.

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Chapter 5, in part is currently being prepared for submission for publication of the material. Keehn, Brandon; Shih, Patricia; Brenner, Laurie; Müller, Ralph-Axel. “Intact Functional Connectivity For an “Island of Sparing” in Autism Spectrum Disorder: An fcMRI Study of Visual Search.” The dissertation author was the primary investigator and author of this paper.

CHAPTER 6

Discussion

The preceding experimental chapters have examined non-social attentional abilities in individuals with ASD and provided evidence for the relationship between attentional anomalies and sociocommunicative impairments in ASD. Specifically, these studies focused on: 1) the sensitivity to novel information (Chapter 2), 2) the efficiency and independence of alerting, orienting, and executive control networks (Chapter 3), 3) and the neurofunctional correlates of enhanced visual search abilities (Chapters 4 and 5) in children and adolescents with ASD. Additionally, each study investigated the relationship between these attentional processes and the level of social and communicative dysfunction in ASD. This chapter begins with an overview of the findings and interpretations from each study and a broader discussion of the results within the context of the literature reviewed in Chapter 1. Next, the results of Chapters 2-5 will be integrated within the context of attentional function in ASD and its purported role in the development of higher-level sociocommunicative impairments. Lastly, potential avenues for future research and possible treatment implications based on the results and conclusions will be discussed.

Experimental Findings

Novelty Processing in ASD

The study presented in Chapter 2 employed behavioral and eye-tracking methods to examine attention to novel onsets in children and adolescents with ASD. In addition, the study sought to evaluate Greenaway and Plaisted's (2005) hypothesis that deficiencies in processing dynamic onset stimuli may be linked to sociocommunicative symptoms in ASD. Two main findings emerged from this study. First, children and adolescents with ASD demonstrated impaired attentional modulation to novel stimuli, which was evident in both their behavioral and eye-movement data. Second, in agreement with Greenaway and Plaisted

(2005), we found that decreased sensitivity to new information was associated with greater sociocommunicative impairment in ASD.

Atypical novelty processing. Dysfunctional novelty processing in ASD, as demonstrated in Chapter 2, is in agreement with previous investigations of novelty processing in ASD as reviewed in Chapter 1. In the preview search paradigm employed in Chapter 2, attending to new information was orthogonal to the participants' task (i.e., reporting the presence or absence of the target, which appeared equally as both a new or an old item). Therefore, reduced sensitivity to novel onsets within the context of the findings presented in Chapter 2 represents impaired bottom-up modulation of attention by new information in individuals with ASD. As discussed in Chapter 1, divergent findings related to novelty detection may be the result of task-specific instructions or context. For example, Dunn and colleagues (2008) demonstrated that in passive listening conditions children with ASD showed reduced MMN amplitude compared to their TD peers, however, no difference in MMN amplitude was found when participants were instructed to actively discriminate auditory stimuli. Based on these findings, the authors concluded that automatic auditory processing is dysfunctional in ASD. Similarly, Gomot and colleagues (2006) found atypically decreased activation to novel information in ASD (relative to TD peers) during a passive task, which is indicative of a default processing state that may reject or ignore novelty. However, in a subsequent study that employed an active task, Gomot and colleagues (2008) found increased activation in ASD in right frontoparietal regions, which may be associated with over-focused attention. These findings highlight the importance of understanding the context in which individuals with ASD evidence novelty processing deficits. In the absence of a top-down attentional set, individuals with ASD may exhibit an insensitivity to any new information; however, when a top-down attentional set is present, the onset of task-relevant

information may capture attention, while task-irrelevant information may be ignored or filtered from further processing.

Prior research has also demonstrated that the P3a component, an electrophysiological index of novelty processing, is abnormal in ASD (reviewed in Chapter 1). Recently, Polich (2007) hypothesized that the P3 component (P3a and P3b) may reflect the inhibition of neural activity for the purposes of transmitting task-related information from the frontal (P3a) to the parietal (P3b) lobe. One model of ASD has hypothesized that the disorder may reflect abnormally increased cortical excitation (Hussman, 2001; Rubenstein & Merzenich, 2003). Therefore, decreased response to novelty (as reflected by smaller P3a amplitudes) may reflect atypical cortical inhibition necessary to adequately stop ongoing activity.

Alternatively, the LC-P3 hypothesis suggests that cortical modulators of the P3 components (lateral prefrontal cortex and temporal-parietal junction) are regulated by the LC-NE system (Nieuwenhuis, Aston-Jones, & Cohen, 2005). Reduced amplitude of the P3a component in ASD could also reflect atypical subcortical modulation by the LC-NE system, which is important for the regulation of tonic and phasic alertness. The hypothesis that atypical subcortical-cortical anatomical connectivity could result in reduced P3a amplitudes in ASD has been put forth previously (Dawson & Lewy, 1989b). Pupil diameter has been shown to correlate with tonic activity of the LC-NE system (Aston-Jones & Cohen, 2005), and more recently, increased tonic pupil size in young children with ASD has been observed (Anderson & Colombo, 2009). Thus, increased pupil diameter may indirectly reflect increased tonic activity of the LC-NE system in ASD. Increased tonic activity of the LC-NE system could result in reduced phasic responsiveness to novel stimuli (as evidenced by reduced P3a amplitude).

Prior studies have demonstrated that novel onsets are uniquely powerful in capturing attention (Jonides & Yantis, 1988). Findings from preview search studies of TD individuals

have demonstrated that sensitivity to new information is associated with increased P3 response (Jacobsen, Schroger, Humphreys, & Roeber, 2001) and increased activation in right temporal-parietal junction (Pollmann et al., 2003). The results of Chapter 2 indicate that bottom-up modulation of attention to novel onsets is disrupted in ASD, and is agreement with previous electrophysiological studies that have demonstrated atypical response to novelty. Together, these results suggest that ASD may be associated with dysfunction of the ventral attentional network, which is responsible for reorienting attention to behaviorally-relevant information.

Association between novelty sensitivity and sociocommunicative impairment. Not only did children and adolescents with ASD exhibit reduced sensitivity to abrupt onsets, but the severity of sociocommunicative impairments within the ASD group was inversely related to onset sensitivity. That is, the less responsive children were to novel information the more impaired their sociocommunicative functioning. This result provides empirical support for theories relating novelty processing deficits to the development of sociocommunicative impairments in ASD (Dawson & Lewy, 1989a; Gold & Gold, 1975; Greenaway & Plaisted, 2005). Deficits in allocating attention to new information could explain a range of associated features in ASD. For example, reduced orienting to name (Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002) or to social and non-social information within their environment (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson et al., 2004) may be the result of this insensitivity to new information. Furthermore, if decreased sensitivity to novel onsets in ASD is the result of new information being perceived as aversive (see Dawson & Lewy, 1989a, for discussion), then certain restricted and repetitive behaviors such as insistence on sameness may also result from atypical novelty processing. Importantly, the association between sensitivity to novel onsets and ASD symptomatology suggests that a lower-level attentional deficit, not specific to the social domain, could have explanatory power with regard to the development of sociocommunicative impairments in ASD.

Efficiency and Independence of Attentional Networks in ASD

As reviewed in Chapter 1, individuals with ASD exhibit impairments and anomalies of each attentional network. The objective of the study presented in Chapter 3 was to use the attention network test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) to examine the efficiency and independence of each attentional network in children and adolescents with ASD. Further, because previous authors have hypothesized that the function of each attentional network may be associated with the development of sociocommunicative deficits, we examined the relationship between the efficiency of each network and measures of sociocommunicative impairment. Results of the study revealed that children and adolescents with ASD 1) exhibited impairments in the efficiency of the orienting and executive control networks, 2) demonstrated greater network interdependence, and 3) showed a significant associations between alerting efficiency and sociocommunicative impairments. Each of these findings will be discussed in turn.

Impaired efficiency of attentional networks. Reduced efficiency of the orienting network in ASD, as demonstrated by the study presented in Chapter 3, is in agreement with the literature reviewed in Chapter 1. Prior studies have examined orienting to both endogenous (gaze or arrow) and exogenous (peripheral onset) cues in both reflexive (50% valid; spatially non-predictive) and voluntary (> 50% valid; spatially predictive) conditions; however, these factors have often been conflated (e.g., using predictive exogenous cues) in previous studies of orienting in ASD (including the study presented in Chapter 3). The combination of these factors results in an interaction between reflexive and voluntary orienting mechanisms that may be different for endogenous and exogenous cues (Olk, Cameron, & Kingstone, 2008). Individuals with ASD have shown consistent deficits in orienting to predictive, exogenous cues (Renner, Grofer Klinger, & Klinger, 2006; Townsend, Harris, & Courchesne, 1996), while demonstrating similar performance to TD individuals on

both predictive (Renner et al., 2006) and non-predictive (e.g., Kylliainen & Hietanen, 2004; Swettenham, Condie, Campbell, Milne, & Coleman, 2003) endogenous cues. Unfortunately, the results from the ANT do not help to disentangle the contributions of reflexive and voluntary orienting. The paradigm used predictive (voluntary orienting) exogenous (reflexive orienting) cues, and can therefore not distinguish whether reduced orienting efficiency in ASD is the result of impaired reflexive or volitional orienting (or their interaction). However, the results add additional evidence that suggests that children with ASD are impaired at processing predictive, exogenous cues. While previous studies have suggested that individuals with ASD may have impaired reflexive and intact voluntary orienting abilities (e.g., Haist, Adamo, Westerfield, Courchesne, & Townsend, 2005; Ristic et al., 2005), future research is necessary in order to elucidate whether orienting deficits observed in the present study are due to specific impairments of reflexive or voluntary orienting abilities or a dysfunctional interaction between these two mechanisms.

In addition to impaired orienting abilities, children and adolescents with ASD also exhibited reduced efficiency of the executive control network. In the case of the ANT, executive control efficiency is a reflection of inhibitory function (as measured by the Eriksen Flanker task). Evidence of impaired inhibitory function in ASD conflicts with the findings reviewed in Chapter 1, in which the majority reported intact inhibitory function in ASD. However, closer examination of executive control results suggests that IQ may play an important role in understanding group differences in executive control abilities. As discussed in Chapter 1, prior studies have reported a relationship between IQ and executive abilities in individuals with ASD. Results from the ANT study replicated these correlations, indicating that lower-functioning individuals with ASD exhibit reduced executive efficiency. Subsequent analyses removing individuals with ASD with below average IQ revealed no group differences in inhibitory function. Results from the present study suggest IQ levels

have important implications for understanding executive impairments in ASD, and indicate relatively intact inhibitory function in individuals with ASD with at least average levels of IQ.

Increased interdependence of attentional networks. Prior studies using the ANT have demonstrated that no correlation between attention network scores exists in TD children (Rueda et al., 2004) and adults (Fan et al., 2002). Although these networks undoubtedly interact, this has been taken as evidence of the relative independence of each attentional network. Similar to these studies, the results of Chapter 3 demonstrate that TD children and adolescents exhibit no significant association between attention network scores. In contrast, the ASD group demonstrated a significant association between alerting and executive control networks. That is, in the ASD group, more inefficient executive control was related to greater alerting inefficiency. One hypothesis is that the association between the alerting and executive control networks could represent compensatory processing in ASD; children with ASD who have more intact and efficient executive control abilities may be able to more efficiently regulate levels of tonic alertness or arousal. Alternatively, as a consequence of arousal dysregulation (reviewed in Chapter 1), individuals with ASD may recruit or rely on executive control mechanisms in order to mediate atypical arousal levels, and as a result, the alerting and executive control networks may become more interdependent. Although speculative, one possibility is that this increased interdependence could result in reduced cognitive resources during periods when regulation of atypical arousal levels is necessary and may explain poorer executive control abilities in ASD.

Previous studies of TD individuals have shown that executive tasks do result in increased arousal levels (Hoshikawa & Yamamoto, 1997). Dysmodulation of arousal in ASD may result in differential task-related increases in arousal and subsequent decreases in performance according to the Yerkes-Dodson law (Yerkes & Dodson, 1908). Additionally, abnormal task-related autonomic response in ASD may result in a redistribution of executive

resources to 1) complete the executive task, and 2) regulate abnormal autonomic response, which results in poorer executive performance. This hypothesis is in accord with the theory put forth by Minshew and colleagues (1997), which posits that that processing deficits in ASD reflect an impairment in processing complex information. And, furthermore, is supported by electrophysiological results from a set switching paradigm, which suggested that poor performance by individuals with ASD may result from aberrant distribution of attentional resources (as indexed by the slow negative wave; SNW) (Ciesielski, Knight, Prince, Harris, & Handmaker, 1995). Prior studies examining the role of arousal on executive control abilities in ASD have demonstrated that poor performance on executive tasks may be related to abnormal modulation of arousal. For example, Raymaekers et al. (2004) (fast stimulus presentation) and Geurts et al. (2009) (slow stimulus presentation) demonstrated that the rate at which stimuli are presented (which modulates arousal levels) differentially affects inhibitory control abilities in individuals with ASD.

High levels of arousal (or stress) result in increased release of norepinephrine and dopamine in the prefrontal cortex, which have been shown to produce impairments in working memory (Robbins & Arnsten, 2009). Previous studies have shown that children and adolescents evidence increased variability of cortisol levels and elevated cortisol after exposure to novel, non-social stimuli (Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006). Increased response and variability of stress response may contribute to poorer performance in more difficult executive tasks (Geurts, Corbett, & Solomon, 2009). This may also explain why individuals with ASD perform worse than comparison groups in standard, experimenter-administered tests of executive function, but at similar levels in computerized versions (Ozonoff, 1995). Interpersonal interaction associated with experimenter-administered tests may add additional stress to a more fragile arousal system in ASD, resulting in impaired test performance due, not to executive impairment specifically, but rather to

dysfunctional modulation of arousal. Ultimately, the use of executive resources to regulate atypical arousal levels may result in greater interdependence between these networks in ASD and poorer performance on more complex executive control tasks.

Association between alerting efficiency and sociocommunicative impairment. Lastly, the results of the study presented in Chapter 3 revealed an association between alerting efficiency and social and communicative deficits in ASD; reduced alerting efficiency was related to increased ASD symptom severity. A reanalysis of these data with a larger sample size (Townsend, Keehn, & Westerfield, in press) showed that, in addition to correlations with a behavioral observational measure of ASD symptom severity (ADOS), alerting scores were also correlated with a parent report measure of social functioning, (Social Responsiveness Scale: Constantino & Gruber, 2005). This additional finding provides added support to the original results suggesting that alerting efficiency is related to social impairment in ASD.

As discussed in Chapter 1, the interaction between tonic and phasic components of the alerting network influence both processing capacity and the breadth of selective attention. Deficient modulation of alertness may correspond to dysfunctional attentional regulation that is characteristic of ASD. Social and communicative difficulties may result from poorer modulation of attention given the dynamic nature of social interactions. Decreased alerting efficiency may result in reduced responsivity to novel stimuli and, similar to the findings from Chapter 2, in inattention to the onset of new information. This is in accord with the theory put forth by Gold and Gold (1975), which hypothesizes that aberrant alerting mechanisms could result in impaired perception of novel incoming information. These authors hypothesize that this impairment in alerting function in children with ASD would result in the inability to attend and respond to significant events within their environment and in the atypical development of social and communicative processes. While the results of Chapter 3 did not find alerting differences between ASD and TD groups, they provide support for this

hypothesis, suggesting that variation in alerting function within the ASD group may play an important role in the behavioral heterogeneity associated with ASD.

Brain Bases for Enhanced Visual Search Abilities in ASD

In contrast to processing deficits discussed in Chapters 2 and 3, Chapters 4 and 5 employed behavioral and fMRI modalities to examine visual search, an area of superior performance in ASD. Chapter 4 examined patterns of activation and behavioral measures of search in a smaller group of children and adolescents with ASD. This study replicated previous behavioral findings of enhanced search abilities (discussed in Chapter 1) and revealed widespread areas of increased activation in ASD. Chapter 5 examined activation and connectivity between regions of interest (ROI) associated with Corbetta and colleagues' (2008; 2002) model of attentional networks for the same visual search task in a larger sample of ASD and TD children and adolescents. Findings from Chapter 5 showed intact task-related functional connectivity in ASD between attentional networks and between attentional networks and visual-perceptual regions. Furthermore, results of Chapter 5 also revealed a relationship between search efficiency and ROI activation and sociocommunicative impairments in ASD. The combined activation, connectivity, and correlational findings for both Chapter 4 and 5 are discussed below.

Differences in region-specific activation. As discussed in Chapter 1, previous studies have shown that individuals with ASD exhibit superior visual search abilities compared to their TD peers, and further, that this skill may be due to enhanced discrimination abilities. In agreement with this hypothesis, eye-tracking studies investigating autistic visuospatial processing strengths have shown that individuals with ASD have shorter fixation durations suggesting that they encode information faster at the locus of attention (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009; Keehn et al., 2009). The fMRI results of the study presented in Chapter 4 may be consistent with these findings suggesting that enhanced

discrimination may underlie accelerated search performance in ASD. Similar to prior fMRI studies investigating visuospatial processing strengths (Lee et al., 2007; Manjaly et al., 2007), results reported in Chapter 4 demonstrate increased activation of posterior occipital-parietal regions in individuals with ASD. This increased activation may reflect enhanced bottom-up modulation of attention, which would be consistent with superior discrimination abilities in ASD.

The findings from the study presented in Chapter 4 also indicate that superior visual search abilities may be derived from enhanced top-down processes as reflected by increased dorsal frontal-parietal activation. Top-down modulation of visual attention can influence stimulus processing by enhancing responses for attended stimuli, filtering irrelevant information, and increasing salience of stimulus features. While previous behavioral studies have suggested that accelerated search in ASD is not related to top-down processes (O'Riordan, 2000), current activation results suggest that increased top-down modulation of attention may also facilitate superior search abilities in ASD. As discussed in Chapter 1, the typical development of visual search abilities may be associated with increased abilities to filter irrelevant distractors. Liss et al. (2006) hypothesized that because individuals with ASD may focus on smaller, local elements of their environment, increased filtering of peripheral information may result in the development of savant-like skills. Therefore, it may be that over-focused attention results both in enhanced visual discrimination and superior filtering abilities in ASD. It should be noted, however, that both whole brain and ROI analyses completed with a larger sample of children and adolescents with ASD did not show distributed increases in activation in ASD. Further work is necessary to understand the region-specific patterns of activation that may contribute to enhanced search in ASD.

Functional connectivity of attention networks. Over the course of the last decade, theories concerning the brain bases of ASD have shifted from a focus on region-specific

localized dysfunction to an emphasis on abnormal neural connectivity (see Belmonte et al., 2004; Rippon, Brock, Brown, & Boucher, 2007, for review). Chapter 5 examined activation-based functional connectivity in individuals with ASD between dorsal and ventral attentional networks and visual-perceptual regions. Contrary to previous reports of task-related functional underconnectivity in ASD, the results of Chapter 5 revealed increased activation-based functional connectivity during performance on a task in which individuals with ASD excel. Specifically, the study found increased mean connectivity between nodes of the ventral attentional network and visual regions, between a node of the dorsal network (right intraparietal sulcus) and visual regions, and between the dorsal network and a region within the ventral network (right temporal parietal junction). The present findings suggest that increased synchronization of activation between attentional networks and visual-perceptual regions may also facilitate search in ASD.

Right temporal-parietal junction de-activation during search has been associated with filtering of irrelevant distractors (Shulman et al., 2007; Wei et al., 2009). However, suppression of right temporal-parietal activation is an effect of this filtering process and not its source. Corbetta et al. (2008) have hypothesized that the dorsal attention network is one potential source of the top-down signal that biases attention for task-relevant information and results in right temporal parietal junction suppression. Thus, increased functional connectivity between the right temporal parietal junction and the dorsal network in ASD may suggest that individuals with ASD achieve their superior performance via enhanced top-down control that biases attention and results in more efficient filtering of task-irrelevant information.

In addition, individuals with ASD exhibited increased connectivity between dorsal and ventral networks and visual-occipital regions. Although the results presented in Chapter 5 did not show previously reported increased activation of occipital cortex, the findings of increased connectivity between these regions suggests that previous reports of superior

performance during visual search in ASD may be associated with greater task-related synchronization between these regions. In sum, the connectivity findings from Chapter 5 suggest that individuals with ASD may achieve superior performance based on increased cooperation between visual-perceptual regions and attentional networks as well as a greater ability to filter irrelevant distractors.

Association between behavioral and neural indices of search and sociocommunicative impairment. Results of Chapter 5 showed an association between a behavioral measure of search efficiency and ASD symptomatology; children and adolescents with ASD who demonstrated greater search efficiency exhibited increased ASD symptom severity. This finding is in agreement with Joseph et al. (2009), who found a relationship between search ability and sociocommunicative impairment in ASD. Furthermore, Liss et al. (2006) reported that a subgroup of children with ASD that exhibited over-focused attention was also the most socially impaired. Lastly, Joseph and colleagues (2002) also demonstrated that greater impairment in social functioning was related to relatively increased non-verbal visuospatial processing abilities in ASD.

Additionally, while Chapter 5 did not find any association between the degree of sociocommunicative impairments and functional connectivity measures, correlational analyses did show an association between the levels of activation and ASD symptom severity. Specifically, increases in activation of the right middle frontal gyrus and reduced activation of left intraparietal sulcus were both related to greater ASD symptomatology. The relationship between right frontal activation and symptom severity is similar to findings reported by Gomot et al. (2008). These authors reported that increased right frontal activation, associated with target-related processing during an auditory oddball task, was correlated with increased social impairment. These authors hypothesized that increased activation may be related to over-focused attention in ASD, which could be beneficial during tasks such as visual search

but have consequences for the adaptive allocation of attention during dynamic social interactions. In addition, Chapter 5 also reported a relationship between decreased activation of the left intraparietal sulcus and increased sociocommunicative impairments in ASD. Prior research has suggested that the parietal lobe may be responsible for creating and maintaining a saliency map, which is used to direct visual attention (Corbetta & Shulman, 2002). Thus, the inverse relationship between activation of the left intraparietal sulcus and sociocommunicative impairment may also implicate a narrower attentional focus. Townsend and Courchesne (1994) demonstrated that parietal abnormalities were associated with a narrower attentional focus and increased perceptual responsiveness. In general, these findings suggest that investigating processing strengths may be of importance to understanding social impairments in ASD, as the development of the mechanisms underlying these superior abilities may also result in social information processing deficits.

Synthesis of Findings

Chapters 2-5 have examined the integrity of attentional subsystems involved in alerting, orienting, and executive control and the relationship between the efficiency of each subcomponent and the degree of sociocommunicative impairment in ASD. Findings from these studies have demonstrated impairments and anomalies in all three attentional networks. Do these findings suggest that individuals with ASD exhibit distinct impairments in specific attentional functions or does this pattern of attentional strengths and weaknesses reflect a common source of attentional dysfunction? These attentional networks have been shown to have some degree of behavioral (Fan et al., 2002), neurophysiological (Fan et al., 2007), and neuroanatomical (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006) independence (see Raz & Buhle, 2006, for discussion). However, interactions between each network are also important for successful and efficient modulation of attention (Callejas, Lupianez, Funes, & Tudela, 2005; Callejas, Lupianez, &

Tudela, 2004; Fan et al., 2009). While these systems may be dissociable in adulthood, the specialization of each independent attentional network is dependent on early interactions between each attentional subcomponent. For example, as reviewed in Chapter 1, infants regulate arousal by shifting attention away from overarousing stimuli, and, in parallel, early arousal regulation influences attentional orienting to novel information. The results of the studies presented in Chapters 2-5 demonstrated a diverse array of abnormalities across all three attentional networks in school-age children and adolescents with ASD. Yet, the studies present a relatively static picture of attentional dysfunction, and, as reviewed in Chapter 1, many of the attentional functions investigated have reached adult-like levels by this age in TD individuals. Could this pattern of attentional strengths and weaknesses present in children and adolescents with ASD be the developmental consequence of earlier attentional impairment?

Chapters 2-5 demonstrate processing impairments in novelty processing and orienting in ASD and processing strengths in visual search. A theory proposed by Liss and colleagues (2006) hypothesizes that hyperarousal generates a state of over-selective attention in ASD. This over-selective attention results in savant-like skills and difficulties shifting attention and inattention to novel information that may appear outside an abnormally narrow attentional spotlight. Viewed through this model, the somewhat disparate findings of processing strengths and weaknesses in ASD from Chapters 2-5 may be the result of a single underlying impairment. That is, reduced sensitivity to novel onsets (Chapter 2), decreased orienting efficiency (Chapter 3), and behavioral and neural indices of enhanced search (Chapters 4-5) may be the result of early hyperarousal in individuals with ASD.

A Developmental Framework

From birth our senses are inundated with information. Attentional mechanisms are responsible for selection of a small portion of information from that deluge. What captures our attention automatically and what we choose to attend to influences the way we experience

and perceive the world around us. Attention has often been considered an associated or secondary deficit within the domain of ASD research; however, the findings laid out in the previous chapters have demonstrated associations between non-social attentional functions and the degree of sociocommunicative impairment in ASD. Findings from these chapters have demonstrated that decreased sensitivity to new information (Chapter 2), reduced alerting efficiency (Chapter 3), and increased search efficiency (Chapter 5) are related to increased symptom severity in individuals with ASD. When viewed from a developmental perspective that incorporates an understanding of typical development, the relationship between these atypical attentional functions and social and communicative deficits form a coherent model. The following section outlines a preliminary framework for understanding the distinct pattern of attentional strengths and weaknesses in ASD, and how these may be related to the development of the triad of impairments and anomalies used to define ASD.

As discussed in Chapter 1, lower-level attentional functions may operate as essential *domain-relevant* mechanisms for the development of higher-level sociocommunicative processes. Such a model has been used by Karmiloff-Smith (2009) to explain delayed language development in Williams syndrome. What follows is a developmental framework that explores the role that atypical attentional processes may have on the emergence of ASD behavioral phenotype. Although, much of the following framework is based on inference rather than direct evidence, the model is consistent with much of the previous research investigating ASD. Despite the fact that ASD is a developmental disorder, very little longitudinal research has been conducted. Therefore many of the links proposed in the current model are suggested, based in part from literature on typical development, and have yet to be tested in infants and children with ASD. A major goal of the proposed model is to provide testable hypotheses for future studies investigating the role of attention on the development of the triad of impairments and anomalies associated with ASD.

Because impaired disengagement is the earliest attentional deficit reported in infants at-risk for ASD (Elsabbagh et al., 2009; Zwaigenbaum et al., 2005) and may be associated with later diagnosis of ASD (Zwaigenbaum et al., 2005), the current framework makes the initial assumption that abnormal disengagement of attention represents a primary disturbance in ASD. Efficient disengagement of visual attention has significant function in two processes: arousal regulation and joint attention. Additionally, and perhaps most speculative, disengagement of attention may also be associated with the development of perceptual biases (see Colombo, 1995, for discussion). Thus, dysfunctional attentional disengagement may trigger a series of developmental sequelae that, in combination with other primary disturbances, result in the heterogeneous phenotypic end-state associated with ASD. Secondary impairments and anomalies in arousal modulation, joint attention, and visual-perceptual processes produce more global deficits in a variety of domains. Each will be discussed in turn.

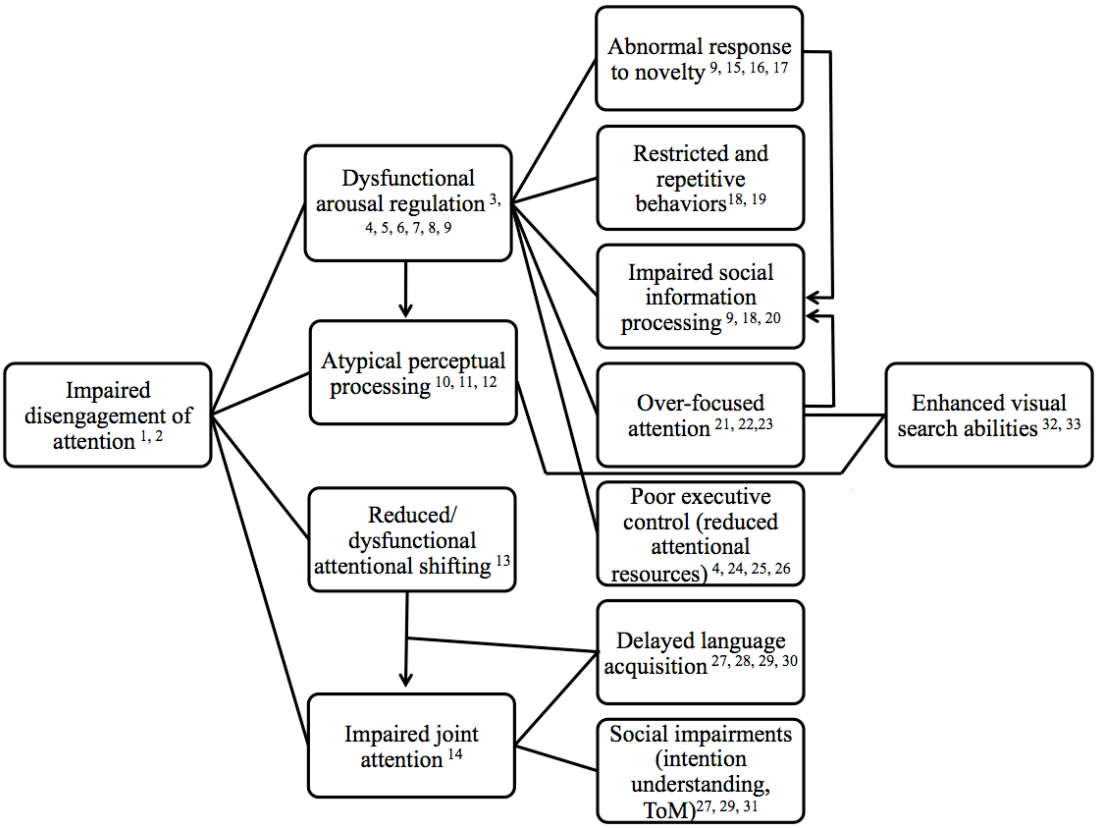

Figure 6.1. Outline of developmental framework. Bold citations represent longitudinal or correlational findings supporting link or association with ASD symptomatology; Italicized citations represent previous theories that have hypothesized link; Underlined citations represent finding from typically developing literature supporting link. [1]Elsabbagh et al., 2009; [2]**Zwaigenbaum et al., 2005**; [3]Anderson & Colombo, 2009; [4]**Keehn et al., 2010**; [5]Field, 1981; [6]Harman et al., 1997; [7]**Johnson et al., 1991**; [8]**McConnell & Bryson, 2005**; *[9]Dawson & Lewy, 1989*; [10]Colombo et al., 1995; [11]Gardner et al., 1993; *[12]Colombo, 1995*; *[13]Courchesne et al., 1994*; [14]**Schietecatte et al., 2011**; [15]**Gomot et al., 2008**; [16]**Keehn & Joseph, 2008**; *[17]Gold & Gold, 1979*; [18]**Garon et al., 2009**; *[19]Hutt et al., 1964*; [20]Pierce et al., 1997; ***[21]Liss et al., 2006*;** [22]Britton & Delay, 1989; [23]Tracy et al., 2000; [24]Ciesielski et al., 1995; [25]Geurts et al., 2009; [26]Raymaekers et al., 2004; [27]**Charman, 2003**; [28]**Dawson et al., 2004**; [29]**Presmanes et al., 2007**; [30]Thrum et al., 2006; [31]**Schietecatte et al., 2011**; [32]**Joseph et al., 2009**; [33]**Keehn et al., in prep.**

Atypical arousal modulation. Shifting attention to distracting stimuli temporally suspends distress in infants (Harman, Rothbart, & Posner, 1997). For example, during face-to-face interactions, infants shift attention away from faces in order to regulate arousal levels (Field, 1981). This suggests that early deficits in disengaging attention may result in the development atypical arousal regulation. The process of arousal modulation in early infancy

involves a dynamic interplay between the internal state of the infant and the level of external stimulation, with a purpose of maintaining a homeostatic state (Gardner, Karmel, & Magnano, 1992). Gardner and colleagues (1992) posit two important hypotheses regarding the relationship between early brain injury and the regulation of arousal and attention. Early atypical brain dysfunction may result in 1) a reduction in the dynamic homeostatic range, and 2) a high level of inherent neural activity (and a diminished level of coherent neural activity).

Evidence reviewed in Chapter 1 showed that individuals with ASD may demonstrate both hyper- and hypoaroused states, which may be a reflection of either dysmodulation of arousal or separate subgroups of individuals with ASD. While prior studies of older children, adolescents, and adults with ASD have demonstrated atypical arousal regulation, a more recent study by Anderson and Colombo (2009) reported that 4-year-old children with ASD exhibit increased tonic pupil size compared to TD children, which is indicative of increased arousal. Furthermore, prospective studies investigating temperament in infants at-risk for ASD have also demonstrated characteristics of over-reactivity and poor arousal modulation (Bryson et al., 2007; Garon et al., 2009). As hypothesized by previous investigators (Dawson & Lewy, 1989a; Gold & Gold, 1975), abnormal arousal level would have developmental consequences in a variety of domains including: 1) abnormal perception of novel information, 2) reduced attention to social information, 3) the presence of restricted and repetitive behaviors, 4) over-focused attention, and 5) reduced efficiency of executive control abilities.

As discussed in Chapter 1, arousal levels impact novelty processing (Barry, Clarke, McCarthy, Selikowitz, & Rushby, 2005). Previous studies of TD infants have demonstrated that decreased efficiency of attentional disengagement is related to greater aversion to novelty (Johnson, Posner, & Rothbart, 1991; McConnell & Bryson, 2005). As a result, atypical arousal modulation (perhaps due in part to impaired disengagement) may result in individuals misperceiving information as non-novel or aversive. As discussed above, multiple studies

(including Chapter 2) using a variety of experimental modalities have shown that individuals with ASD have dysfunctional novelty processing. Furthermore, the evidence from Chapters 2 and 3 have demonstrated that an inefficient alerting system and decreased sensitivity to new information are both related to increased sociocommunicative deficits. Previous authors have hypothesized that due to an unstable arousal system, the novel, dynamic, and complex features of social stimuli and unpredictable nature of social interactions may be overarousing to individuals with ASD (Dawson & Lewy, 1989a). Because infants use attentional shifts to regulate arousal during early face-to-face interactions (Field, 1981), impaired disengagement during these interactions could lead to hyperarousal in infants and toddlers with ASD. Following repeated instances of overarousal during early social interactions, social information may become aversive and individuals with ASD may no longer perceive social interactions as intrinsically rewarding. This would be agreement with a previous theory of ASD that suggests that social dysfunction may result from an abnormal reward system associated with social stimuli (Dawson et al., 2002). Interestingly, this idea may be in line with results that demonstrate that attention to faces in 6 month old at-risk infants is not associated with later diagnosis (Young, Merin, Rogers, & Ozonoff, 2009). Perhaps inattention to faces and atypical face processing develops later due to earlier overarousal during face-to-face exchanges.

Also in agreement with the hypothesis that the complex nature of social stimuli may be overarousing, Pierce and colleagues (1997) found that the social perception abilities of children with ASD was relatively more impaired with an increasing number of social cues. The authors reasoned that, if dysfunctional social cognition is due to impaired perception of social information, then trials with redundant social information (i.e. multiple cues) should improve task performance in ASD; however, if ASD social deficits are related to an attentional impairment, then task performance should improve in conditions with reduced

attentional requirements (i.e. single cue condition). In accord with the latter hypothesis, the authors reported similar performance between ASD and comparison groups for the single cue condition, but impaired performance for the ASD group for the multiple cue conditions. The authors suggest that dysfunctional arousal modulation may influence attentional capacity for social information, resulting in poorer social perception in situations with redundant social information (i.e., multiple cues).

In addition to deficits in communication and reciprocal social interaction, ASD is defined by the presence of restricted and repetitive behaviors (see Turner, 1999, for review). Hutt and colleagues (1964) hypothesized that chronically hyperaroused individuals with ASD may engage in repetitive behaviors in order to reduce levels of arousal. Furthermore, they hypothesized that aversive response to novel objects or events may exacerbate atypically increased arousal levels, resulting in rigid patterns of behavior and insistence on sameness. A more recent study has demonstrated an association between restricted and repetitive behaviors and atypical sensory responsiveness (Gabriels et al., 2008), and is in agreement with findings relating arousal level to increased repetitive behaviors (Colman, Frankel, Ritvo, & Freeman, 1976). Interestingly, Garon and colleagues (2009) recently demonstrated that an observational measure of restricted and repetitive behaviors was related to measures of temperament, including attentional shifting and activity level. Because impaired disengagement of attention may result in overarousal, the persistent use of repetitive movements may reflect an alternative means of "self-soothing" (Liss et al., 2006, p. 167) for individuals with ASD. The domain of restricted and repetitive behavior has received relatively little attention in research, however, these findings suggest that atypical disengagement and hyperarousal may play a part in the presence of these behaviors.

Liss and colleagues (2006) have hypothesized that over-focused attentional style in ASD may be the result of hyperarousal. Additionally, the authors hypothesize that over-

focused attention in these individuals would result in an amplification of sensory information at the locus of attention (and reduced processing of information outside the atypically narrow attentional focus). Prior studies with TD adults suggest that increased arousal may result in a narrowed attentional focus and increased suppression of peripheral information (Britton & Delay, 1989; Tracy et al., 2000). Over-focused attention may help explain the superior performance of individuals with ASD (as compared to their TD peers) on a variety of visuospatial tasks (see Dakin & Frith, 2005, for review). Additionally, previous eye-tracking studies have demonstrated reduced fixation durations in children and adolescents with ASD (Joseph et al., 2009; Keehn et al., 2009), indicative of enhanced perceptual discrimination at the locus of attention. Lastly, Liss and colleagues (2006) demonstrated that a subgroup of individuals with ASD that exhibited this over-focused profile were the most socially impaired. This is congruent with the findings of Joseph et al. (2009) and those reported in Chapter 5, which demonstrated that enhanced visual search ability was related to increased sociocommunicative impairments in children with ASD.

Abnormal modulation of arousal could also have important consequences for the development of efficient executive control abilities. Previous research has demonstrated that early measures of executive function are related to novelty processing (Sheese, Rothbart, Posner, White, & Fraundorf, 2008) and self-regulation (Gerardi-Caulton, 2000). Due to early impairments in arousal regulation in ASD (as the result of impaired disengagement of attention), individuals with ASD may recruit or rely on effortful control or self-regulation in order to mediate the states of both hypo- and hyperarousal. Based on these assumptions, individuals with ASD would exhibit impairments in executive function during states of both hypo- and hyperaroual states. In addition, we might expect neurocognitive networks associated with arousal and executive control to become more interdependent in ASD. The former hypothesis is supported by findings that indicate that executive deficits are related to

arousal modulation (discussed above). The later hypothesis is supported by evidence from Chapter 3, which demonstrated increased interdependence between alerting and executive control networks in ASD. These hypotheses may help explain the contradictory findings within the ASD executive control literature.

Although studies have yet to directly link disengagement difficulties to aberrant arousal regulation in ASD, prior studies have demonstrated these deficits in the same individuals (Bryson et al., 2007; Watson et al., 2007). Disengagement of attention has an important regulatory function early in development. If this function is impaired, atypical arousal and responsivity to environmental stimuli could be a possible developmental consequence. As outlined above, deficits within these functions could have implications for a broad array of domains associated with ASD, including novelty processing, social attention, over-focused attention, restricted and repetitive behaviors, and executive function.

Impaired joint attention abilities. Joint attention is the coordinated attention between an individual and his/her social partner. Or, more simply stated it is "looking where someone else is looking" (Butterworth & Jarrett, 1991, p. 223, as cited in Moore & Corkum, 1994). Prior research has shown that children with ASD demonstrate impaired joint attention abilities (see Bruinsma, Koegel, & Koegel, 2004, for review). Early joint attention may depend on the attention-capturing characteristics of the environmental stimulus and on changes in head/gaze direction of the caregiver (Butterworth & Grover, 1990). These early joint attention abilities are based on more basic attentional mechanisms (Frischen, Bayliss, & Tipper, 2007) and begin to develop between 6 and 12 months, continuing to mature into the second year of life.

One such mechanism necessary for successful joint attention is the ability to efficiently disengage attention from the current focus in order to shift and engage the object or event at the locus of the caregiver's attention (Hood, Willen, & Driver, 1998). Impaired

disengagement of attention in at-risk infants has been demonstrated within the second half of the first year of life (Elsabbagh et al., 2009; Zwaigenbaum et al., 2005), a period in which joint attention abilities begin to appear. Recently, Schietecatte and colleagues (2011) reported that a relationship exists between attention disengagement and joint attention abilities in ASD. Children with ASD that disengaged attention faster made more joint attention initiations. Because the study did not include a TD comparison group, the authors were unable to determine whether disengagement was slowed in ASD; however, others have reported disengagement difficulties within this age range (Landry & Bryson, 2004).

Importantly, joint attention abilities in TD infants and toddlers have been linked to both language development and understanding the psychological states of others (Carpenter, Nagell, & Tomasello, 1998). Multiple studies have also linked early joint attention skills to later language (Charman, 2003; Dawson et al., 2004; Presmanes, Walden, Stone, & Yoder, 2007; Thurm, Lord, Lee, & Newschaffer, 2007) and social functioning (Charman, 2003; Presmanes et al., 2007; Schietecatte et al., 2011) abilities in children with ASD. Early difficulties disengaging attention could have important implications for successfully responding and initiating joint attention in infants with ASD. In accord with this idea, Charman referred to joint attention abilities as "not a starting point but merely a staging post in early sociocommunicative development" (Charman, 2003, p. 321). Perhaps early disengagement difficulties reflect a possible origin for joint attention difficulties and its developmental consequences.

Atypical perceptual processes. Because role of disengagement on the development of perceptual processing biases is currently the most speculative consequence of impaired disengagement, evidence in support of this hypothesis is limited. As briefly reviewed in Chapter 1, individuals with ASD have been shown to excel at a variety of visuospatial tasks relative to their TD peers. Two theoretical models, Weak Central Coherence (Happe & Frith,

2006) and Enhanced Perceptual Functioning (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006), have been proposed to explain these "islets of ability." Both theories posit that enhanced ASD performance is due, at least in part, to a local processing bias. That is, individuals with ASD are biased towards local or featural information rather than global properties of a stimulus. Previous research investigating the mechanisms underlying fixation durations in TD infants has demonstrated that "long lookers" tend to show a local processing bias (Colombo, Freeseman, Coldren, & Frick, 1995). Colombo (1995) hypothesized that one possible explanation for increased fixation durations (i.e., "long lookers") may be impaired disengagement of attention associated with immature development of the brain regions associated with the orienting network. These infants may find it difficult to shift attention away from salient local features of stimuli. However, at this point, whether impaired disengagement leads to the development of local processing bias and enhanced abilities in ASD remains complete conjecture. Future research investigating the relationship between disengagement abilities and local-global processing biases in both TD and ASD populations is necessary in order to establish this link.

In addition to disengagement abilities, Gardner and Karmel (1995) have demonstrated that level of arousal also interacts with infants' preference for certain stimulus characteristics; increased infant arousal results in increased looking to less intense stimuli, whereas decreased infant arousal leads to increased looking to more intense stimuli. Therefore, level of arousal (which, again, is influenced by the efficiency of attentional disengagement) may have important implications for the development of visual-perceptual preferences or sensitivities, and may contribute to atypical perceptual processes in ASD.

Summary

As was said by Gold and Gold, "using attentional mechanisms as our fulcrum, we may be able to understand the global nature of autism and appreciate the clinical

manifestations of this disease" (Gold & Gold, 1975, p. 76). The proposed developmental framework attempts to explain the diverse and heterogeneous nature of ASD by exploring the hypothesis that atypical attentional disengagement may be one of many primary impairments associated with the disorder. In summary, in infants with ASD, a primary disturbance in the ability to efficiently disengage attention results in the abnormal development of arousal regulation, joint attention abilities, and, perhaps, visual-perceptual processes. In turn, aberrant arousal regulation may result in atypical response to novelty, restricted and repetitive behaviors, reduced attention to social information, over-focused attention, and poor modulation of executive abilities. Dysfunctional joint attention abilities produce delays in language acquisition and deficits in understanding the intentions of others. Lastly, impaired disengagement may result in the development of atypical visual perception characterized by local or detailed processing bias.

Autism spectrum disorder is diagnosed based on impairments and anomalies in three core domains: language, reciprocal social interactions, and restricted and repetitive behaviors. Although, much of this framework is based on inference rather than direct evidence, I have proposed a developmental scenario in which a primary disturbance in non-social, attentional disengagement may be used to explain the unique and diverse behavioral phenotype of ASD. This is not meant to imply that impaired disengagement represents the *only* primary behavioral disturbance in ASD, rather it may be one of many early aberrant behaviors that alter typical developmental trajectories in ASD. Finally, this model has focused only on behavior, however, it should be noted that the development of these behaviors interact in a multidirectional manner with gene expression and brain development throughout the course of development.

Future Directions

This Chapter has reviewed the results and implications of the studies presented in Chapters 2-5, integrated these findings within the context prior research investigating attention in TD and ASD individuals, and presented an emerging framework for understanding the role of attention in the development of ASD. This section will present potential avenues for future research, which could further elucidate the etiological significance of early attentional impairments in ASD as well track the developmental trajectories of attentional functions in ASD. In addition, this section will discuss possible treatment implications based on the experimental results and the proposed developmental framework.

Future Research

Typical development of attentional systems undergoes rapid change during the first year of life. The maturation of alerting, orienting, and executive control functions continues to mature into the school-age and adolescence period. Fifty years of attention research on ASD has largely given us static pictures of a developmental disorder after these attentional mechanisms have reached adult-like levels in TD individuals (present studies included). While these studies have provided important information regarding the attentional strengths and weaknesses in ASD, understanding whether these impairments are a cause or a consequence of ASD remains to be determined. More recently, prospective studies of infants at-risk for ASD have provided researchers with a glimpse of early attentional function and its relationship to the development of the disorder. These studies have provided a nascent understanding of the emergence of the autistic phenotype. However, important questions remain: 1) *How does attention set (i.e., top-down modulation of attention) affect the processing of new information?* Results from Chapter 2 suggest that children with ASD exhibit impaired bottom-up modulation of attention; however, results from neuroimaging studies show intact or enhanced processing of novel information when individuals with ASD are given an active task (i.e., identify the target). Future research investigating novelty

processing in ASD should include conditions with and without a top-down attentional set to examine how task-relevant and task-irrelevant information captures attention in ASD; 2) *Do early arousal levels influence sensitivity to new information and does this impact sociocommunicative development?* A consistent finding across multiple experimental methodologies indicates that individuals with ASD demonstrate dysfunctional novelty detection. However, the question that remains to be fully answered is *why* individuals with ASD do not respond in a typical fashion to the onset of novel information and how this aberrant response develops. The results from Chapter 3 demonstrated that inefficient alerting was related to greater ASD symptom severity, and results from Chapter 2 demonstrated that insensitivity to new non-social information is related to greater sociocommunicative dysfunction. Future prospective studies of at-risk infants should investigate how early arousal levels influence sensitivity to new information later in life to determine if atypical arousal regulation results in abnormal novelty processing and deficits in sociocommunicative functioning; 3) *What specific orienting mechanisms are impaired in ASD?* Similar to previous studies of orienting abilities in ASD, results from Chapter 3 demonstrate reduced orienting efficiency. However, studies thus far have failed to isolate underlying impairment(s) associated with orienting deficits as these studies have conflated reflexive and voluntary orienting abilities. Future studies should examine the contributions of reflexive and voluntary orienting abilities separately and together in order to isolate the unique contributions to orienting impairments in ASD; 4) *How might autistic processing strengths (examined in Chapters 4 and 5) develop, do these superior abilities arise from early dysregulation of arousal resulting in over-focused attention, and how are they related to sociocommunicative dysfunction?* The results from Chapter 4 and 5 replicated previous findings of enhanced performance and demonstrated that superior search abilities may be related to increased activation and connectivity of both top-down and bottom-up attentional mechanisms. Further,

they demonstrated, similar to previous studies, that behavioral and neural indices of search are related to ASD symptom severity. Future studies should examine the relationship between early arousal regulation and attentional disengagement and the development of visuospatial processing biases, and how over-focused attention may impact the development of social information processing skills in ASD. And finally, and perhaps most importantly; 5) *Are autistic social and communicative impairments developmental sequelae of abnormal disengagement of attention?* Resolving this question has important implications for both the early identification of infants at-risk for ASD and for early interventions. Evidence from the experimental studies presented in Chapters 2-5 suggests that attentional abnormalities are present and that they are related to impairments in higher-level sociocommunicative processes. However, longitudinal behavioral and physiological research with young children at risk for autism, complemented by pediatric neuroimaging studies, will help to resolve the question of causality. Such research can tell us whether domain-general impairments in attention play a role in the development of autistic sociocommunicative deficits.

Lastly, and more generally, future research endeavors would also benefit from a cross-syndrome perspective (see Cornish, Scerif, & Karmiloff-Smith, 2007, for example). Tracking the developmental trajectories of attentional functions in variety of developmental disorders may help to understand how divergences due to attention impairments result in atypical developmental trajectories and how these specific impairments ultimately result in the unique phenotypic outcomes.

Clinical Implications

The studies presented above demonstrate that an association exists between non-social attentional function and the level of sociocommunicative impairment in ASD. Nevertheless, as discussed in Chapter 1, while the focus of this dissertation has been on the role of attention in the development of ASD, this is not meant to imply that impaired attentional modulation is

the only primary disturbance. Rather, the goals of understanding whether dysfunctional attentional processes are of etiological significance in ASD is two-fold. If early attentional impairments play a causal role in the development of ASD then 1) attentional deficits may be used as an early neuro-behavioral marker that can be used to identify infants at-risk for ASD and 2) the development of attention-targeted early interventions may remediate abnormal developmental trajectories and improve outcomes in children with ASD.

Early identification of infants at-risk for ASD is of paramount importance for successful early intervention. Thus far, prospective research investigating socioemotional function in infants at-risk for ASD has not revealed significant patterns of early social dysfunction (see Rogers, 2009, for review). Thus, current diagnostic tools may rely on abnormal behaviors that appear on a more consistent basis later in development. If attentional abnormalities are one of the first characteristics that distinguish infants who are later diagnosed with ASD, then diagnostic tools should employ an approach that emphasizes these attentional deficits. These tools may result in earlier diagnosis and treatments, which has important implications for successful early intervention that may help reduce the atypical development trajectories in ASD.

Furthermore, if early attentional dysfunction (e.g., disengagement difficulties) are a primary impairment in ASD, then the development of early attention-targeted interventions may help ameliorate the development of higher-level sociocommunicative deficits. Posner and Rothbart (2005) have suggested that early attentional interventions may be a useful tool to promote cognitive and social development. Because children with ASD evidence early attentional impairments, interventions targeted at atypical attentional networks may produce generalized improvement across multiple domains. For example, attention training programs have been shown to reduce pathological attention biases, resulting in generalized benefits and improved outcomes in adults with Generalized Anxiety Disorder (Amir, Beard, Burns, &

Bomyea, 2009). Previous research has demonstrated that early interventions have been successful in improving joint attention abilities in children with ASD (Kasari, Freeman, & Paparella, 2006; Whalen & Schreibman, 2003). Perhaps training the constituent functions of joint attention earlier in development (disengaging, shifting) may have important implications for both the development of joint attention skills but also arousal regulation. Regardless of whether atypical attention plays a causal role in the development of sociocommunicative deficits, integrating knowledge associated with attentional strengths and weakness may improve current intervention strategies (see Koegel, Shirotova, & Koegel, 2009, for example).

Finally, each attention network discussed in Chapter 1 and examined in Chapters 2 -5 has been associated with the function of distinct neurotransmitters. Therefore, elucidating network-specific impairments in attention (e.g. orienting) may assist in directing pharmacological treatments and provide an outcome measure for their impact. Previous research investigating pharmacological interventions targeting neuromodulators associated with specific attention networks have had some success (see Lam, Aman, & Arnold, 2006, for review).

Understanding the abnormal developmental trajectories of attentional function in ASD from infancy to adulthood will make it possible to identify the contribution of atypical attentional functions to the development of social and communicative deficits. Moreover, if atypical attention processes specific to ASD manifest themselves prior to the onset of language delay or reciprocal social impairments, then they may be unique markers that will enable clinicians to identify and treat individuals at-risk earlier and ultimately result in increased positive outcomes. Finally, if these dysfunctional attentional processes lead to the development of aberrant sociocommunicative functioning, then early interventions focused on treating and training efficient and adaptive modulation of attention may be more efficacious for reducing the severity of core deficits in sociocommunicative functioning.

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