

**Atypical attention and autism spectrum disorders (ASD)
symptoms: Development and interactions with learning and
memory**



Brianna Doherty

New College

University of Oxford

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Abstract

This thesis investigates the nature of atypical attention in relation to autism spectrum disorders (ASD) symptoms, as well as the mechanisms by which it may relate to social impairment. First, does atypical non-social attention predict social impairment over time in the context of ASD, suggestive of a causal relationship? Second, if atypical attention plays a role in social impairments in ASD, what is the mechanism?

With regards to the first question, longitudinal data with children at familial risk for ASD demonstrated a unidirectional relationship between non-social attention and social functioning at the cognitive level: 2-year-old non-social attention predicted 3-year-old face recognition, but there was no relationship between 2-year-old face popout and 3-year-old visual search. Additionally, we examined the relationships between ASD and ADHD symptoms over three years in children at high risk for both—children with fragile X syndrome. This allowed for investigating atypical non-social attention and social impairment at the symptoms level, again revealing a unidirectional relationship with ADHD symptoms predicting ASD symptoms over time but not the reverse. These findings suggest that atypical non-social attention may contribute to social impairment.

With regards to the second question, a novel eye-tracking and visual search paradigm revealed how task irrelevant social stimuli in natural scenes can lead to poorer subsequent explicit spatial contextual memory and altered memory-guided attention orienting—effects that were moderated by autistic traits and social anxiety within a neurotypical population. Further, this research found cross-sectional development, comparing 6-10-year-old children to young adults, and investigated the neural markers of social stimuli's effect on memory. These studies suggest a possible mechanism whereby a reduced social attention bias could lead autistic individuals to learn and remember less about people and the social world and result in social impairment.

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Chapter 1: Introduction

Autism Spectrum Disorders (ASD)

In the 1940s, on opposite sides of the world, Leo Kanner in the United States (1943) and Hans Asperger in Austria (1944) independently described a condition based on the observation of particular children in their clinics who previously would have been described as “schizophrenic” or “feeble-minded”. These children demonstrated a unique profile of social interaction impairments, communication deficits, narrow obsessive interests, and monotonous repetitive behaviors. The claims that these children represented a unitary syndrome were further validated by an epidemiological study of children living in Camberwell, London (Wing & Gould, 1979), which led to the classification of the triad of symptom domains that has been used to define ASD until very recently (American Psychiatric Association, 1994). Each of these domains will be discussed in turn, and these descriptions are informed by the four sources cited here.

Social interaction

The heart of this domain lies in an inability to develop and sustain meaningful peer relationships that are appropriate for the individual’s developmental level. Autistic individuals may desire to form friendships, yet fail to do so due to difficulty with engaging in reciprocal social behaviors or emotions. They may also avoid social contact altogether. In general, autistic individuals demonstrate a lack of spontaneous seeking to share enjoyment with others, as well as atypical nonverbal social behaviors, including eye gaze and facial expression (Asperger, 1944; Kanner, 1943; Wing & Gould, 1979).

Social communication

This domain is defined by a delay in, or in more impaired individuals a total lack of, spoken language. There may be stereotyped (echolalia) or idiosyncratic language. Even in individuals with adequate languages abilities, there may be marked impairment in the ability to initiate or sustain conversations (Ricks & Wing, 1975).

Imagination (repetitive interests/activities)

The final aspect of the triad is demonstrated by an insistence on sameness and strict adherence to routines, stereotyped and repetitive motor behaviors (e.g., hand flapping), as well as persistent preoccupations and narrow interests (Wing, Gould, Yeates, & Brierley, 1977; Wing, Yeates, Brierley, & Gould, 1976). For example, an autistic individual may become distressed if traffic complications lead to taking a different route to school. Autistic individuals may also be obsessed with particular interests, including train timetables or dates.

What is new with DSM-V

In May of 2013, the American Psychiatric Association (APA) released a new diagnostic manual with updated diagnostic criteria for autism (American Psychiatric Association, 2013). Whereas in the previous manual (DSM-IV), individuals could be diagnosed with four separate disorders: autistic disorder (most similar to Kanner's classification), Asperger's syndrome (closely related to autistic disorder, but with no language delay), childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS), DSM-V incorporated these into one encompassing autism spectrum disorder (ASD). This spectrum emphasizes the continuum of symptoms from mild to more severe and focuses on individual differences in needs. In addition, as opposed to the traditional triad of symptoms, the DSM-V

delineated two symptoms groups: social-communication deficits and restricted interests and repetitive behaviors (Figure 1). Additionally, the new criteria included hyper- or hyporeactivity to sensory input within the restricted interests and repetitive behaviors group, which had previously been absent in the diagnostic manual.

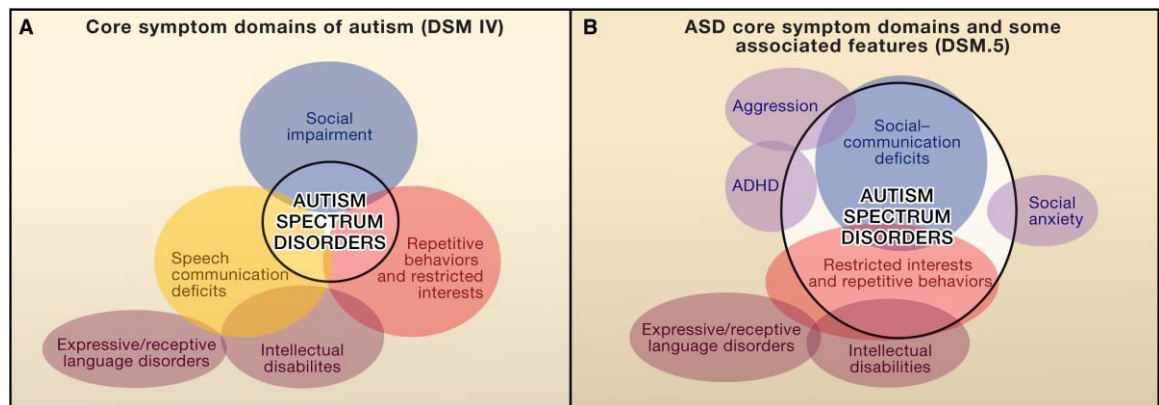


Figure 1. Changes to the core symptom groups for autism spectrum disorders (ASD) from DSM-IV to DSM-V. The two core symptom groups in DSM-V are social communication impairments and restricted interests, repetitive behaviors and atypical sensory perception (adapted from Lord, 2011).

Prevalence

The most recent estimates suggest that ASD is common, with a prevalence of 1 in 100 children in the UK (G. Baird et al., 2006) and 1 in 68 individuals in the US (Centers for Disease Control and Prevention, 2012). ASD is more common in males than females, with an often-quoted estimated ratio of 4:1 (Fombonne, 2003; 2009). However, this estimate has been decreasing more recently (e.g., Kim et al., 2011), and may be exaggerated due to misdiagnosis and a more subtle presentation in women and girls that leads to a lack of referral (e.g., Gould & Ashton-Smith, 2011; Rynkiewicz et al., 2016).

Cognitive Theories of ASD

Due to the unique profile of symptoms and seemingly disparate symptom groups described above, a desire for parsimony led cognitive psychologists early on to focus on underlying cognitive causes for the disorder. Much of this research led to the development of unified cognitive theories of ASD. While these theories have been challenged in many ways, the debates stemming from them have urged researchers to continually reappraise their understanding of ASD, and has allowed for important progress in the study of ASD in particular and neurodevelopmental disorders in general. Here we discuss three prominent accounts, although there are certainly others.

Theory of mind

The term “theory of mind” was coined by Premack and Woodruff (1978) in reference to their research with chimpanzees. These authors stated that an individual with a theory of mind “imputes mental states to himself and to others” (Premack & Woodruff, 1978, p. 515). A theory of mind thus relates to the understanding that other people have mental states (i.e. intentions, beliefs, desires), which can be different from one’s own mental states, as well as different from the true state of the world (see Wellman, Cross, & Watson, 2001 for a meta-analysis).

Due to the prominent impairments in social understanding in ASD, one of the first unified cognitive theories of autism suggested that the primary deficit in the disorder was that autistic individuals lack a theory of mind (Baron-Cohen, Leslie, & Frith, 1985; U. Frith, 1989a; Leslie & Frith, 1987). Baron-Cohen and colleagues (1985) reported that 80% of autistic children tested failed the classic Sally-Anne false belief task (Baron-Cohen et al., 1985), compared to only 15% of neurotypical children. In

false belief tasks such as this, participants are asked to predict the actions of someone who holds a false belief. These tasks are therefore considered to test for the presence of a theory of mind (Wimmer & Perner, 1983). In addition, the researchers suggested this failure was not due to intellectual disability, as only 14% of children with Down's syndrome failed the task, despite lower average mental age compared to children with ASD.

This seminal study led to work investigating the theory of mind module in the ASD brain as well. Several studies suggested that the temporo-parietal junction is recruited when neurotypical children and adults think about other's mental states (Kobayashi, Glover, & Temple, 2007; Perner, Aichhorn, Kronbichler, Staffen, & Ladurner, 2006; Saxe & Kanwisher, 2003; Saxe & Wexler, 2005). These findings have led some to argue that this region represents a specialized theory of mind module (Saxe & Wexler, 2005), although this is not without debate (Mitchell, 2008). Similar studies have reported atypical activity in these theory of mind brain regions, as well as disruptions to the connectivity between regions, in autistic individuals (Kana, Keller, Cherkassky, Minshew, & Just, 2009; Mason, Williams, Kana, Minshew, & Just, 2008). Some researchers have taken such findings as evidence of a specific disruption in the theory of mind brain module alongside an intact general processing ability (U. Frith, 2001), mirroring earlier, behaviorally based theories that implicated a broken theory of mind module as the cause of the core symptoms of ASD (Leslie, 1992).

However, there are several arguments against a specific deficit in theory of mind as the primary cause of ASD. First of all, while the majority of autistic individuals fail false belief tasks, there are still some who pass. If theory of mind is truly the core deficit in ASD, and false belief tasks are accurately assessing theory of mind, surely no autistic individuals should pass these tests. Although some have counteracted this point by

reporting that even fewer individuals with ASD pass more complex second order false belief tasks (Baron-Cohen, 1989) or more naturalistic tests of theory of mind (Happé, 1994), these arguments still do not address the second point: that children with ASD may not be passing theory of mind tests for reasons other than a lack of theory of mind.

For example, false belief and other theory of mind tasks require executive function capabilities, including memory capacity to remember the sequence of events in stories, and the ability to inhibit prepotent responses (such as the actual location of the marble in the Sally-Anne task). Indeed, there is evidence to suggest a relationship between executive functions and theory of mind in autistic children, with a primary deficit in executive functions rather than theory of mind (Pellicano, 2007; 2010), as well as in typical development (Devine & Hughes, 2014). In addition, these tasks often have excessive linguistic demands (Astington & Baird, 2005; Milligan, Astington, & Dack, 2007), and children with ASD struggle with verbal understanding and communication as described above. In fact, there is a reported relationship between language skills and the ability to pass false belief tasks in autistic children (Tager-Flusberg & Joseph, 2005). Although some autistic individuals who pass traditional false belief tasks fail a more implicit, spontaneous task akin to the seminal study by Onishi and Baillergeon (2005), which reduces the language and executive function demands, this task still suffers from the first critique raised above. In this study, 8 out of the 19 autistic individuals made “correct” anticipatory looks (Senju, Southgate, White, & Frith, 2009).

Third, the theory of mind theory does not take into account other symptoms associated with ASD, including the sensory difficulties highlighted in the DSM-V and the restricted interests and repetitive behaviors. If impaired theory of mind is the core deficit in ASD, it should comprehensively explain the other impairments present in the disorder as well.

Fourth, although proponents of the theory of mind theory often discuss a theory of mind module in the brain that is “broken” (U. Frith, 2001; U. Frith, Morton, & Leslie, 1991), other seminal work suggests that the brain develops these modules over developmental time, and does not contain them from birth. For example, the interactive specialization framework posits that some cortical regions begin with broad functionality and only specialize with experience and interactions with other cortical regions (M. H. Johnson, 2000; 2011). Moreover, this framework has been applied to the social brain specifically (M. H. Johnson, Grossmann, & Cohen Kadosh, 2009). Within this framework, it seems unlikely that an innate theory of mind module exists within the brain. However, an interactive specialization framework of autism suffers from the other critiques of the theory of mind theory of autism described above—how might it be utilized to encompass both the social and non-social symptoms of ASD?

Weak central coherence

While the theory of mind theory of ASD is domain-specific, describing a deficit in a theory of mind module, other major cognitive theories are more domain-general. For example, the weak central coherence (WCC) theory of ASD suggests that the primary impairment is in global processing—in integrating parts into a whole (U. Frith, 1989b; U. Frith & Happé, 1994). This theory developed from the observation of an uneven cognitive profile in ASD, with clear deficits across subtests in verbal IQ but enhanced performance in the block design subtest of performance IQ, which requires the ability to easily segment wholes into their component parts (Shah & Frith, 1993). The WCC theory was further supported by enhanced performance on the Embedded Figures Task in ASD (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983), in which participants must detect a shape that is embedded within a picture (e.g., a triangle that is

hidden in a line drawing of a grandfather clock) (Witkin, 1971). Additional evidence comes from limited vulnerability to visual illusions in autistic individuals—illusions which require the integration of perceptual features (Happé, 1996).

Unlike the theory of mind theory, early versions of the WCC theory attempted to account for many of the diverse symptoms seen in ASD. In addition to explaining the narrow interests and repetitive behaviors, due to increased processing of the parts at the expense of the whole, researchers argued that the WCC theory explains the social and language impairments evident as well. Frith (1989b) argued that the ability to understand another person's mental states (theory of mind) and communicate effectively requires integrating many pieces of information, including facial expression, tone of voice, context, etc. A weakness in this ability would be disruptive to developing a theory of mind and may lead to the social impairments seen in ASD. A similar argument could be made for language deficits in ASD (Happé, 1995).

Despite these strengths, evidence for the WCC theory of ASD has been mixed, with several studies finding evidence to question it. For example, a popular task for assessing WCC is the Navon task (Navon, 1977), in which participants are shown a large letter made up of smaller letters and asked to identify the local (small letter) or global (large letter) target. Although the WCC theory posits that children with ASD will demonstrate more of a local bias compared to typically developing children, several researchers have found a global bias in both groups (Ozonoff, Strayer, McMahon, & Filloux, 1994; Plaisted, Swettenham, & Rees, 1999). Further undermining the WCC theory, a global processing bias/lack of local processing bias, similar to that found in neurotypical individuals, has been found in autistic individuals in other experimental tasks as well (Mottron, Burack, Iarocci, Belleville, & Enns, 2003; Mottron, Burack, Stauder, & Robaey, 1999; A. D. Smith, Kenny, Rudnicka, Briscoe, & Pellicano, 2016),

and a recent meta-analysis reports that there does not appear to be an overall global processing deficit in ASD, rather autistic individuals differ in their global processing speeds (Van der Hallen, Evers, Brewaeys, Van den Noortgate, & Wagemans, 2015).

Executive dysfunction

Another domain-general theory of ASD is the executive dysfunction theory. Executive functions (EFs) are defined as “the ability to maintain an appropriate problem-solving set for attainment of a future goal” (Welsh & Pennington, 1988, p. 201), including inhibiting prepotent responses, planning action sequences, and maintaining task representation in memory. Executive functions have been researched extensively with neurotypical individuals, due to their clinical and societal relevance (Miyake & Friedman, 2012; Miyake et al., 2000)

Investigations into executive dysfunction in ASD were originally guided by the “frontal metaphor” in which the behavioral profile of a disorder resembles lesions to the prefrontal cortex (Pennington & Ozonoff, 1996). Damasio and Maurer (1978) suggested similarities between the core symptoms of ASD and the behavioral profiles of individuals with frontal lobe lesions. This initial suggestion was subsequently followed up with experimental work, demonstrating that autistic individuals perform poorly on executive function tasks, including the Wisconsin Card Sorting Task (Ozonoff & McEvoy, 1994; Prior & Hoffmann, 1990) and the tower of London task (Hughes, Russell, & Robbins, 1994). Although the frontal metaphor spurred important experimental work, it is crucial to note that cases of adult brain damage can only be a distant metaphor in describing neurodevelopmental disorders (D. V. Bishop, 1997; Karmiloff-Smith, 1998).

Importantly, the executive dysfunction theory may explain a range of ASD symptoms, including both the social communication impairments and restricted interests and repetitive behaviors. For the social impairments, as discussed above, there is a strong relationship between executive functions and theory of mind (Pellicano, 2007; 2010). Communication impairments similar to those seen in ASD (e.g., difficulties with metaphors) are also seen in frontal lobe patients (Wiig, Alexander, & Secord, 1988), suggesting a link between executive dysfunction and language deficits in ASD. While this comparison suffers from the same limitations of neuropsychology with regards to neurodevelopmental disorders discussed above, developmental work gives stronger support to the link between executive functions and language in neurotypical development (e.g., Nation, Marshall, & Altmann, 2003). With regards to narrow interests and obsessive behaviors, it is easy to see how difficulty with set-shifting and perseverative behaviors, as is found when using the WCST, may be related to these symptoms.

Despite these strengths, there is one main argument against the executive dysfunction theory of ASD. There are several other disorders that present with executive dysfunction, including attention deficit/hyperactivity disorder (ADHD) (Biederman et al., 2004), Tourette syndrome (E. L. Harris et al., 1995), fragile X syndrome (Munir, Cornish, & Wilding, 2000b), and others. In order for there to be a unified cognitive theory of ASD, the cognitive impairment(s) must be specific to ASD (Karmiloff-Smith, 2009). Some researchers have addressed this critique by suggesting that different disorders reflect different developmental onsets of executive dysfunction (Pennington & Ozonoff, 1996). Others have focused on more specific components of executive functions, for example investigating set-shifting in particular (Hughes et al., 1994).

Implications of early cognitive theories of ASD

One implication of the debate surrounding these theories is the clarification that a unified cognitive theory of ASD (or any neurodevelopmental disorder) must meet certain criteria, which the above theories do not. In particular, the implicated cognitive cause must 1) be primary (early WCC does not uniquely contribute to later ASD symptoms: Pellicano, 2013b), 2) be universal (not every autistic individual fails theory of mind tasks: Baron-Cohen et al., 1985), and 3) be specific (children with ADHD are also reported to experience executive dysfunction: Biederman et al., 2004). Additionally, if one posits a particular cognitive disruption to be the *only* disruption, it must account for both the social and non-social symptoms of the disorder. The inability to find cognitive theories of ASD that meet this criteria has led some researchers to argue that the search for parsimonious single-deficit accounts is futile, and autism is better characterized by fractionable impairments (Happé & Ronald, 2008). However, there is also evidence contrary to the hypothesis that different cognitive atypicalities explain distinct features of ASD. Longitudinal evidence suggests that domain general skills, and executive functions in particular, uniquely predict both social *and* non-social symptoms of ASD (Pellicano, 2013b). As this debate is ongoing, we take a middle ground, focusing on the developmental implications of a specific cognitive atypicality in ASD, regardless of whether it satisfies the criteria outlined here, as opposed to arguing its unitary/fractionable nature with respect to a particular theory.

Atypical attention in ASD

Most relevant to the current thesis, the final cognitive contributing factor to be discussed here is that of atypical attention. Of note, the overlap and distinctions from other cognitive factors discussed (in particular, executive functions) need to be

evaluated carefully, as they are not necessarily mutually exclusive, and we will do so where relevant as we move through the thesis. Even from the early days of ASD, clinicians and families alike have noted atypical attention in autistic individuals. Kanner (1943) himself noted impairments in attention, arousal and responsiveness. From this and other observations, early researchers (M. S. Gold & Gold, 1975), as well as more recent (Keehn, Müller, & Townsend, 2013), have posited that atypical attention is the critical and primary deficit in ASD. Attention constrains what is perceived and further processed from the environment; therefore, atypical attention may have cascading effects over developmental time, including in social communication and interaction, ultimately contributing to the emergence of the ASD phenotype. It is this hypothesis that we address in the current thesis.

Although several aspects of attention have been considered atypical in ASD in the literature, including the arousal, orienting, and executive control systems posited by Posner and Peterson (1990) (see Keehn et al., 2013 for a review of these systems in ASD), the current thesis will focus on selective attention in particular. There are several reasons for this focus. One reason is that selective attention is perhaps the most studied in the ASD literature (see below). Another, more theoretical reason is that while EFs have been reported to predict social and non-social symptoms in ASD, above and beyond contributions by WCC and theory of mind skills (as discussed above: Pellicano, 2013b), a review of EFs in preschool children suggests that early selective attention processes predict EFs in later childhood (Garon, Bryson, & Smith, 2008). Selective attention may therefore serve as a good candidate to test developmental implications in ASD, as it may be a rate limiting factor on the development of EFs in ASD (Pellicano, 2012). Importantly, this work highlights how atypical attention and executive dysfunction in ASD are not necessarily mutually exclusive. Finally, one of the most

extensive reviews of atypical attention in ASD to date posits that attentional disengagement, a component of selective attention, is the primary deficit in a developmental framework of atypical attention in ASD (Keehn et al., 2013).

Selective attention in ASD

The study of attention in psychology is an old one, and those who study selective attention often bring to mind the quote by William James:

Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others. (James, 1890, pp. 403-404)

Humans are incapable of processing all of the stimuli available in the environment, therefore selective attention is necessary to prioritize one aspect of the environment at the expense of others. In short, it is the ability to suppress distracting, irrelevant information in order to effectively process relevant information.

Lovaas and colleagues (1971) were some the earliest to investigate selective attention experimentally in ASD. In their study, children were rewarded for responding to multisensory, complex stimuli. The study found that although autistic children were equally likely to attend to any of the three modalities that made up the stimuli to facilitate learning, they tended to focus on only one modality compared to neurotypical and intellectually disabled children who were able to attend to several. Researchers argued that this was due to over-selectivity within autistic children (Lovaas et al., 1971). The mechanism of this over-focused, over-selective attention is, however, a matter of debate. While some researchers argue that over-selectivity in ASD is due to “tunnel vision,” (Rincover & Ducharme, 1987) such that the attentional spotlight is contracted and fewer stimuli are processed from the outset (which is potentially related to atypical

parietal and cerebellar activity, J. Townsend, Courchesne, & Egaas, 1996a; J. Townsend, Harris, & Courchesne, 1996b), others suggest that autistic individuals struggle to broaden an existing attentional spread—once attention is “zoomed in,” they struggle to “zoom out” again (Mann & Walker, 2003). Regardless of the mechanism, it is interesting to note that over-selectivity may interact with other aspects of selective attention. Attention shifting, and in particular attentional disengagement, has been reported as impaired in ASD, with slower disengagement, or “sticky fixation” often described (Elsabbagh et al., 2013; 2009; Kawakubo et al., 2007; Landry & Bryson, 2004; Zwaigenbaum et al., 2005). A broader spread of attention may be required in order to disengage and redirect attention to a new object in the environment, thus over-selective attention may hinder this ability (Mann & Walker, 2003).

In contrast to the over-selectivity account of selective attention in ASD, other researchers have suggested under-selectivity. Using a forced-choice reaction time task, Burack (1994) found that autistic individuals were significantly slowed by distractors when compared to neurotypical and intellectually disabled individuals, despite those distractors being relatively far from target stimuli. The author suggested this finding reflects an inefficient attentional lens that is overly extended as opposed to overly focused (Burack, 1994). Similarly, other researchers have found an impaired ability to filter out distractors in selective attention tasks, paired with altered neurophysiological responses as recorded by electroencephalography (EEG) (Ciesielski, Courchesne, & Elmasian, 1990).

Although these contrasting findings are certainly confusing for attaining a unified framework of atypical attention in ASD, a third theory of selective attention in ASD may account for these discrepancies. Remington and colleagues (2009) used a perceptual load task, in which participants viewed a ring of letters and were asked to

identify a target (either an X or and N) present on the screen. At the same time, outside of the ring was a distractor letter, either one that had no association to the target (compatible) or one that was the alternative distractor (i.e. the X if the target was an N, incompatible). The assumption was that if distractors were processed, RTs would be slower in incompatible compared to compatible trials. Crucially, perceptual load was manipulated by increasing the number of non-target elements in the central ring (or, set size), to see if this would affect distractor processing. Remington and colleagues (2009) found that, although overall RT and errors did not differ between ASD and neurotypical groups, autistic individuals demonstrated greater perceptual capacity. This was indexed by the finding that, even at higher set sizes, the ASD group showed a difference in RT between compatible and incompatible trials, suggestive of distractor processing (Remington et al., 2009). Although one could argue that differential RTs to incompatible versus compatible trials could be the result of interference with response selection as opposed to perceptual processing, higher perceptual capacity at higher loads in ASD has since been replicated using a signal detection task as well (Swettenham, Lavie, & Remington, 2012). The authors argue that an enhanced perceptual capacity in ASD may explain conflicting findings of over- and under-focused selective attention in ASD. Proponents of a perceptual load account suggest that enhanced capacity results in indiscriminate and mandatory processing of more stimuli in ASD, and where the stimuli processed are task relevant performance will be enhanced and where stimuli are irrelevant performance will be impaired (Swettenham et al., 2012).

Visual search in ASD

One such selective attention task where performance is enhanced in ASD is visual search. Visual search tasks are perhaps the most commonly used tool to assess

selective attention in general, but also in ASD in particular. Visual search has classically been investigated under two conditions: feature search and conjunctive search. In feature search, targets “pop out” and therefore stimuli can be processed in parallel, whereas in conjunctive search, stimuli are thought to be processed serially (Treisman & Gelade, 1980). Plaisted, O’Riordan and Baron-Cohen (1998) were the first to investigate visual search in autistic children. They found that in the feature search condition, there was no difference between the ASD and neurotypical groups, in that search time remained constant with increasing distractor numbers. However, in the conjunctive search condition, while neurotypical children demonstrated the expected increase in search time with increasing distractors, autistic children’s search times increased very little. Such enhanced visual search ability has since been replicated many times, including with verbal IQ and age-matched neurotypical children (O’Riordan & Plaisted, 2001), adults (O’Riordan, 2004), toddlers (Kaldy, Kraper, Carter, & Blaser, 2011), and most recently with 8-month old infants (Cheung et al., 2016; Gliga, Bedford, Charman, Johnson, BASIS Team, 2015a).

There have been several competing theories of enhanced visual search in ASD. Although an early suggestion was that perhaps autistic individuals have a greater inhibition of return, in which they are better able to remember distractor locations and therefore avoid revisiting them, other researchers have reported this to be unlikely. Joseph and colleagues (2009) tested ASD and neurotypical groups in both dynamic and static visual search tasks, hypothesizing that if enhanced search in ASD was related to memory for distractors it would not be seen in dynamic search in which distractors moved. However, autistic children demonstrated enhanced search in both conditions. Instead, in light of studies suggesting that target-distractor discriminability is the rate-limiting factor in visual search (Duncan & Humphreys, 1989), the majority of

researchers have suggested that perceptual enhancement underlies superior search (Kemner, van Ewijk, Van Engeland, & Hoge, 2008; O'Riordan & Plaisted, 2001; Plaisted et al., 1998; Swettenham et al., 2012). On the other hand, other researcher have reported no correlation between perceptual discrimination ability and enhanced visual search (Brock, Xu, & Brooks, 2011), although caution is warranted because the researchers investigated ASD traits in a neurotypical population as opposed to autistic individuals. In contrast to the enhanced perception account, another theory suggests that atypical attention, in particular overly focused attention (as discussed above), may be responsible for superior visual search skills in ASD (Kaldy, Giserman, Carter, & Blaser, 2016; Keehn et al., 2013). While some researchers attribute this over-selective attention to impaired attentional disengagement (Keehn et al., 2013) others suggest hyperphasic arousal is responsible (Kaldy et al., 2016).

Social attention in ASD

In addition to the more domain-general aspects of selective attention, it is also important to note that some stimuli hold privileged attentional status, and appear to be selected automatically and involuntarily. It is helpful to return to the words of William James, perhaps less often quoted than his general definition of attention, but equally tantalizing:

In involuntary attention of the immediate sensorial sort the stimulus is either a sense-impression, very intense, voluminous, or sudden; or it is an instinctive stimulus, a perception which, by reason of its nature rather than its mere force, appeals to some of our congenital impulses... these stimuli differ from one animal to another, and what most of them are in man: strange things, moving things, wild animals, bright things, pretty things, metallic things, blows, blood, etc. (James, 1890, pp. 416-17).

For neurotypical individuals, a vast literature describes how social stimuli, and faces in particular, hold a special perceptual and attentional status. Studies have reported

increased attention to face configurations in newborn babies, which led to the proposal that infants are born with an innate structural representation of faces (Morton & Johnson, 1991). Neuroimaging has extended these findings to suggest brain areas (e.g., Puce, Allison, Asgari, Gore, & McCarthy, 1996) as well as single cells (e.g., Perrett, Hietanen, Oram, & Benson, 1992) specialized for processing faces. In addition to perceptual sensitivity, faces have also been reported to play a special role in selective attention (Vuilleumier, 2000; Vuilleumier, Armony, Driver, & Dolan, 2001), including in change-detection tasks (Ro, Russell, & Lavie, 2001) and cueing tasks (Langton & Bruce, 1999). Moreover, distractor faces are reported to show interference effects in visual search even under high perceptual load, suggesting automatic, and potentially mandatory processing (Lavie, Ro, & Russell, 2003).

Although early anecdotal and clinical evidence suggested that autistic individuals attend differently to social stimuli, a more nuanced understanding of social attention was not originally possible due to technological constraints. Before eye-tracking technology, one of the earliest empirical studies of social attention found evidence of face avoidance when using black and white drawings and behavioral coding (Hutt & Ounsted, 1966). However, a review of studies between 1966 and 1994 found mixed results with regards to gaze avoidance (Buitelaar, 1995). With the advent of eye-trackers and their integration into cognitive psychology research, the study of selective attention in ASD for social stimuli specifically has become an intensely studied topic.

The primary method of investigating atypical social attention in ASD with eye-tracking has utilized free viewing of social stimuli, including isolated static images (e.g., C. J. Anderson, Colombo, & Shaddy, 2006), static naturalistic scenes (e.g., Riby, Hancock, Jones, & Hanley, 2013), dynamic videos (e.g., Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011), as well as live interactions (e.g., Noris et al., 2011).

These studies have reported that autistic children and adults are less engaged by social stimuli, and when attending to social stimuli, attend less to the eyes and more to the mouth or body (see Papagiannopoulou, Chitty, Hermens, Hickie, & Lagopoulos, 2014 for a meta-analysis with children). Autistic adults and adolescents scan social scenes in an atypical manner (e.g., Klin, Jones, Schultz, & Volkmar, 2003; Norbury et al., 2009), and process facial attentional cues differently, although the developmental mechanisms underpinning these outcomes remain unclear (Nation & Penny, 2008).

The majority of studies, however, has instructed free viewing of stimuli, or has made faces/people the focus of attention. A different method of studying atypical social attention is investigating social *distraction* when people are *not* the targets of attention. For example, neurotypical children take significantly longer to find a target in a simple graph search when there is a face as a distracting item than when there is an equivalent non-face distractor, whereas there is no difference between trials in children with ASD (Riby, Brown, Jones, & Hanley, 2012). In light of the study described above in which distractor faces show interference effects in visual search even under high perceptual load for neurotypical individuals (Lavie et al., 2003), the lack of distractor effects for faces in autistic children is suggestive of an absence of automatic, involuntary processing of faces in ASD.

Despite this seemingly straightforward distinction between a privileged attentional status for social stimuli in neurotypical individuals that is absent in autistic individuals, there are several important theoretical caveats to discuss. First, is it important to discuss the origins of social attention, and in particular potential bottom-up contributions to a bias towards social stimuli. With regards to neurotypical individuals, although it has been suggested that infants have an innate preference for face configurations in particular (Morton & Johnson, 1991), other researchers have found

this preference to be derived from a domain-general bias towards top heavy stimuli, and not specific to faces (Cassia, Turati, & Simion, 2004). Similarly, although some researchers have argued for domain-specific perceptual processes for faces that are housed in dedicated brain regions (Kanwisher, 2000), this theory has been challenged by research demonstrating that expertise to non-face objects recruits the same processes and brain areas as face perception in neurotypical individuals (Gauthier & Tarr, 1997; Tarr & Gauthier, 2000). These findings have led researchers to suggest that non-face specific attentional proclivities present at birth may produce the specialization for faces seen later in development (Cassia et al., 2004). Extrapolating this reasoning, the lack of a privileged attentional status for faces in ASD may similarly arise from non-face specific perceptual and/or attentional mechanisms, rather than face-specific processing atypicalities, a point to which we will return in our general discussion.

Indeed, there are many non-specific lower-level perceptual differences between ASD and neurotypical groups that may contribute in a bottom-up manner to an atypical social attention bias. There is evidence that autistic individuals differ in color perception under certain conditions (Cranwell, Pearce, Loveridge, & Hurlbert, 2015; Franklin, Sowden, Burley, Notman, & Alder, 2008; Franklin et al., 2010; Fujita, Yamasaki, Kamio, Hirose, & Tobimatsu, 2011). Motion perception has also been reported to be atypical (Bertone, 2005; Bertone, Mottron, Jelenic, & Faubert, 2003; Manning, Charman, & Pellicano, 2013; Manning, Tibber, Charman, Dakin, & Pellicano, 2015; Milne et al., 2002; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005; J. Spencer et al., 2000). Finally, luminance contrast has been suggested to be atypical in ASD (McCleery, Allman, Carver, & Dobkins, 2007). Importantly, these differences can even be seen at 6-months of age (McCleery et al., 2007), which suggests they may be present at birth, or at least very early in development. How “low-level” these perceptual

differences are is, however, up for debate. While some researchers suggest that perceptual differences arise at the level of the retina (E. Ashwin, Ashwin, Rhydderch, Howells, & Baron-Cohen, 2009), others argue that it is rather the *interpretation* of sensory input that leads to altered perception, and more specifically the presence of attenuated Bayesian priors in ASD (Pellicano, 2013a; Pellicano & Burr, 2012). Although several researchers have suggested that such early atypical low-level perceptual processing may drive the atypical social attention seen in ASD (McCleery et al., 2007; Mundy, Sullivan, & Mastergeorge, 2009; Senju & Johnson, 2009), none to our knowledge have investigated this experimentally.

Importantly, when using a computational method that combines multiple features of visual perception (pixel level, e.g., color; object level, e.g., size; and semantic level, e.g., face) to calculate the salience of features in natural images, Wang and colleagues (2015) found that autistic individuals weighted low-level properties (e.g., color, contrast) higher and object and semantic properties lower in salience than neurotypical individuals. There is therefore evidence that what is visually salient for autistic individuals differs from neurotypical individuals based on perceptual properties. For this reason, it is important to have carefully controlled stimuli when investigating social attention, or lack thereof, in ASD.

Moreover, although the studies above have reported reduced attention to social stimuli compared to neurotypical individuals, they often do not compare attention to social stimuli to equally salient non-social stimuli. While some studies utilize scrambled or inverted faces as control comparison stimuli, these stimuli are unnatural, particularly when included in natural scenes. Ecological validity with respect to stimuli is incredibly important when investigating social attention in ASD, as researchers have raised concerns due to reported differences between stimulus types (Hanley, McPhillips,

Mulhern, & Riby, 2013; Speer, Cook, McMahon, & Clark, 2007). However, without comparing attention to non-social stimuli, it is impossible to distinguish whether attention is reduced to social stimuli in particular, or to neurotypically salient stimuli in general, as is suggested by the study by Wang and colleagues (2015).

The current methodology

In order to test the impact of atypical attention in ASD within a developmental framework, in which early non-social atypical attention may have cascading effects over development that lead to social impairments, two questions must be addressed, each with differing timescales of study. First, in order for attention to be a causal deficit in ASD, it must be primary to the social impairments and/or demonstrate a unidirectional relationship to social impairments. One way to investigate this is to explore the relationship(s) between atypical attention and social impairment longitudinally in ASD. Does atypical non-social attention predict social impairment over time? Second, if atypical attention plays a role in social impairment in ASD, what is the mechanism? Does a reduced social attention bias lead to social impairment through learning and memory, such that this atypical bias leads autistic individuals to learn and remember less about people and the social world? It is these two questions this thesis addresses, and to which we now discuss in turn.

Relationships between atypical non-social attention and social impairments over time

One method to determine if atypical attention in ASD contributes to the hallmark social impairments seen in the disorder is to demonstrate the primacy of atypical attention over development. Causes must come before effects, and therefore

atypical attention must come before social impairments in order for it to be a causal deficit. A review of prospective longitudinal studies suggests that social impairments and attention impairments show a similar developmental trajectory in infants at risk for ASD, with both appearing within the first year of life (E. J. H. Jones, Gliga, Bedford, Charman, & Johnson, 2014). This review led the authors to propose that attention is not a primary deficit. However, this may be because it has proved difficult to investigate these questions experimentally with younger infants, as well as because these younger infants are difficult to recruit, as the authors themselves highlight. Another way to investigate the potentially causal nature of atypical attention in ASD is to look at relationships over developmental time. A unidirectional relationship over time in which attention predicts social impairments but not vice versa would provide preliminary evidence in support of a causal role of atypical attention.

For this reason, in addition to taking an in-depth and novel approach to investigating visual search in young children at familial risk for ASD in Chapter 2, Chapters 2 and 3 investigate relationships between atypical non-social attention and social impairment over developmental time in two populations at high risk for ASD: children at familial risk (due to having an older sibling diagnosed with ASD) and children with fragile X syndrome.

Mechanism by which atypical social attention affects social impairment

A second method for investigating the role of atypical attention is to look mechanistically at how social attention (or lack thereof) may operate within a learning framework. While domain-general selective attention may play an early role in a developmental framework of ASD, and may contribute to an altered, more domain-specific social attention bias (as described above), an altered social attention bias may

further contribute in a cascading manner to the development of social interaction impairments.

First, given the caveats described above, it is necessary to carefully control for the perceptual characteristics of stimuli when investigating social attention in ASD and to compare social and non-social attention directly, in order to confirm diminished social attention in this population. While some researchers have compared attention to social stimuli to attention to non-social stimuli that are semantically relevant to circumscribed interests autistic children often have (trains, clocks, airplane, etc.) (Sasson & Touchstone, 2014; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011; Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008), or other non-social objects determined to be subjectively salient (Wilson, Brock, & Palermo, 2010), these studies did not control for the low-level perceptual characteristics of their stimuli. Moreover, the one study to our knowledge that has controlled for these perceptual properties, such that they compare equally salient social and non-social stimuli, did so with isolated images (S. Wang et al., 2014). Using isolated images reduces ecological validity and has been shown to be problematic in the social attention ASD literature, as described above. Chapters 4, 5 and 6 attempt to address these concerns by controlling for low-level perceptual salience in naturalistic social and non-social scenes.

Second, if a lack of a privileged status for social stimuli is a part of the atypical attention cascade that contributes to ASD, how does this atypical attention bias lead to the social interaction impairments that define the disorder? One potential mechanism is that reduced attention to social stimuli may result in an individual learning and remembering less about people and the social world, which could lead to difficulty in social interactions. Chapters 4, 5 and 6 investigate this hypothesis with neurotypical adults and children within an experimental learning paradigm. This paradigm allows for

assessing the functional consequences of a social attention/inattention bias on learning and memory, as well as subsequent attentional orienting based on these experimentally induced memories. The hope is that this work will allow for further investigation with autistic individuals.

Chapter 2: Visual search organization and autism symptoms: Relation to concurrent social cognition and infant predictors in young children at risk

*This chapter, excluding the 2-year-old data and 3-year-old face recognition task, is in its first revision at Developmental Science: **Doherty, B., Charman, T., Johnson, M. H., Scerif, G., Gliga, T. & the BASIS team (revise and resubmit)**. Visual search and autism symptoms: What young children search for and co-occurring ADHD matter.*

Candidate contribution: The candidate was not involved in the design of these experiments, nor in the recruitment of participants/collection of data at any timepoint. The candidate contributed to this study by: creating a novel analysis strategy, implementing data analysis, and writing up the report. Ethical approval in addition to that granted to the cohort study as a whole (below) was not required for this collaborative data analysis, as determined by the British Autism Study of Infant Siblings (BASIS; www.basisnetwork.org) protocol.

Introduction

Enhanced visual search ability is one of the most consistent findings in the autism spectrum disorder (ASD) literature. Beginning with the seminal paper by Plaisted, O’Riordan, and Baron-Cohen (1998), superior visual search has been documented in ASD in toddlerhood (Blaser, Eglington, Carter, & Kaldy, 2014; Kaldy et al., 2011; 2016). Superior visual search during infancy has also been reported to predict the severity of later ASD symptoms and ASD clinical diagnosis (Cheung et al., 2016; Gliga et al., 2015a). However, superiority in visual search is not always replicated, with

task design and sample characteristics as important factors (e.g., Hessels, Hooge, Snijders, & Kemner, 2014; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015).

With regard to task design, previous publications suggest that the nature of target/distractor differences might affect whether participants with ASD show superiority in visual search. For example, superior search is observed more often when target and distractors are perceptually similar (e.g., Plaisted et al., 1998). Based on what we know about the phenotypic profile of ASD, one can make further predictions about when search would put them at an advantage. For example, ASD advantage might be less prominent when conceptual properties, rather than perceptual properties, guide search.

Previous research with neurotypical individuals suggests that searching for a superordinate category (“footwear”) as opposed to a basic category (“boots”) proves generally more difficult (Maxfield & Zelinsky, 2012; Schmidt & Zelinsky, 2009). This is probably due to the lack of specificity that helps to guide visual search to realistic, complex objects; the longer time required to verify that the target is a member of the superordinate category; and the tendency to combine instances of a category into a prototype that may have little overlap with specific search target exemplars (Hout & Goldinger, 2015; H. Yang & Zelinsky, 2009; Zhang, Yang, & Samaras, 2006). Furthermore, neural measures indicate that search guided by categorical attentional templates is not as efficient as item-specific search (Wu et al., 2013). Given the evidence for difficulties with making inferences based on category knowledge in ASD (see Naigles, Kelley, Troyb, & Fein, 2013 for thorough discussion), it is possible that difficulties with searching for targets belonging to a superordinate category (e.g., “animals”) as opposed to a basic category (e.g., “a cat”), will be exacerbated in participants with this disorder. In most real life situations, search will be guided by not

only low-level perceptual characteristics of searched-for items (Duncan & Humphreys, 1989; Treisman, 1991), but also their higher-level categorical characteristics (Maxfield & Zelinsky, 2012; Schmidt & Zelinsky, 2009). Unfortunately, the majority of the visual search literature in ASD to date has used simple targets and distractors, as for example by requiring participants to find a target ‘o’ amongst ‘x’ distractors, which prevents investigation of conceptual influences.

Another relevant aspect of search paradigms is the number of targets. Most commonly, visual search tasks showing an advantage in ASD have required locating one single target amongst distractors. In contrast, everyday selective attention often requires us to navigate a complex visual world to locate many items. Is ASD search superiority apparent when not one, but multiple targets have to be found? Multiple target search may require additional cognitive skills, such as good organization and planning. Based on the proposal that ASD traits confer “systematicity” (Baron-Cohen, 2009), one might expect better search organization and therefore even better search performance in multiple target displays. The relatively small literature investigating visual search as the ability to cancel / find multiple targets (“cancellation” henceforth) is mixed, with some finding poorer performance in ASD and others with no differences compared to neurotypical individuals (Goldstein, Johnson, & Minshew, 2001; Minshew, Goldstein, & Siegel, 1997; Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998). However, these studies used relatively simple measures of performance, such as omission and commission errors and time to completion. Pellicano and colleagues (2011) employed more complex measures of search paths, instructing children to find a single hidden target amongst multiple search locations in a “foraging room.” They reported less optimal (longer distance to the target) and less systematic (reduced search consistency from trial to trial) search in children with ASD compared to neurotypical

children. Thus, despite being potentially better at initially spotting targets, children with ASD might not take the most optimal route to scanning and sampling the environment, which would mitigate their strengths when faced with richer environments.

Alternatively, *poor* search organization might actually be the result of common co-occurring conditions. Clinical ADHD or ADHD traits have been described in children with ASD and in populations at-risk for ASD (Ozonoff et al., 2014; Simonoff et al., 2008). Approximately 20% of ASD children aged 7 in the UK meet the diagnosis of ADHD and vice versa (G. Russell, Rodgers, Ukoumunne, & Ford, 2014). ADHD has been linked to poorer visual search with single targets (Mullane & Klein, 2008), as well as more disorganized large-scale search (Rosetti et al., 2016).

In the current study we investigate whether the search superiority conveyed by ASD traits holds when the nature of the target/distractor distinction is varied in a multi-target cancellation task. We asked these questions in a sample of 3-year-olds who are at familial risk for ASD due to having an older sibling with this disorder, as well as in low-risk controls. About 20% of younger siblings develop ASD themselves (Ozonoff et al., 2011) and another 20% will manifest subthreshold ASD symptoms and/or developmental delay (Messinger et al., 2013), as well as other conditions, such as increased ADHD traits (Ozonoff et al., 2014). The broader spectrum of symptom severity in at-risk populations offers a unique opportunity to investigate relationships between search skills and dimensional phenotypic measures, in accordance with recent research domain criteria (Insel et al., 2010). A recent shift away from categorical diagnostic boundaries and towards a continuous characterization of childhood psychopathology has been motivated by both clinical and genetics research (Plomin, Haworth, & Davis, 2009). This framework suggests that qualitative disorders, including ASD and ADHD, are in fact the extremes of a continuum of behavior seen across the

entire population, as opposed to separate groups of individuals with clear diagnostic boundaries. Researchers are therefore encouraged to move beyond group comparisons to investigate relationships with symptoms as continuous variables, as we do in the current study.

In addition to the open questions regarding search discussed above, two other important questions are: 1) how does search organization relate to concurrent social impairments (if at all) and 2) what are the relationships over longitudinal time between attention (measured by search cancellation at 3-years) and social cognition in children at familial risk for ASD? Although several studies have shown longitudinal relationships between early attention abilities and later ASD symptoms (Elison et al., 2013; Elsabbagh et al., 2013; Gliga et al., 2015a; Wass et al., 2015; Zwaigenbaum et al., 2005), no studies to our knowledge have investigated the longitudinal relationships between attention abilities and more specific social impairments at the cognitive level. Although one study investigated the contributions of both attention and social cognition atypicalities at 14 months to later ASD symptoms, finding an independent, additive relationship rather than one predicting the other (Bedford et al., 2014), investigations would greatly benefit from a longitudinal analysis of the attention and social cognition measures themselves. Does early non-social selective attention predict later social impairments? Or do early social impairments predict later non-social attention in our multi-target cancellation task? Or is there no relationship between the two over time? A unidirectional relationship whereby early attention predicts later social impairments but not vice versa would be suggestive of a primary deficit of attention in ASD, as others have hypothesized (Keehn et al., 2013), and addresses a question posed in the current thesis.

We tested 3-year-olds at both high and low familial risk for ASD in three search conditions: exemplar search (look for a specific example of a cat amongst artifacts), perceptual search (look for a specific example of a dog amongst chairs/tables perceptually similar to dogs), and categorical search (look for several examples of animals amongst artifacts). We hypothesized that, compared to exemplar search, high ASD symptoms and/or an ASD diagnosis would relate to poorer performance in categorical search and yet potentially enhanced performance in perceptual search, consistent with the previous literature in fully diagnosed, older ASD cases. We also predicted that co-occurring ADHD symptoms would relate to poor performance and disorganized search.

Methods and materials

Recruitment

Participants took part in a prospective longitudinal study of infants at high- and low- familial risk for autism (hereafter, HR and LR) recruited as part of the British Autism Study of Infant Siblings (BASIS; www.basisnetwork.org). Families enroll when their babies are younger than 10 months of age, and they are invited to attend multiple research visits until their children reach 3 years of age. At the time of enrolment, none of the infants had been diagnosed with any medical or developmental condition. 116 HR participants and 27 LR participants took part in the longitudinal study. The data presented in this paper was collected during the last two visits, at 2 and 3 years of age. 106 HR (60 boys, 46 girls) and 25 LR (14 boys, 11 girls) participants contributed data to this study. Participant characteristics for those included in analyses are below. The London Research Ethics Committee approved this study (Ref: 06/MRE02/73) and all parents provided written informed consent.

HR infants had at least one older sibling (hereafter, proband) with a community clinical diagnosis of ASD (96 probands were male, 10 were female). An expert clinician confirmed proband diagnosis based on information using the Development and Well Being Assessment (DAWBA; R. Goodman, Ford, Richards, Gatward, & Meltzer, 2000a) and the parent-report Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003). Most probands met criteria for ASD on both the DAWBA and SCQ ($n = 72$). While a small number scored below threshold on the SCQ ($n = 8$), no exclusions were made, due to meeting threshold on the DAWBA and expert opinion. For 8 probands, data were only available for the DAWBA and for 16 probands data were only available for the SCQ. For 3 probands, neither measure was available aside from parent-confirmed local clinical ASD diagnosis at intake. Parent-reported family medical histories were examined for significant medical conditions in the proband or extended family members, with no exclusions made on this basis.

Infants in the LR control group were recruited from a volunteer database. Inclusion criteria included full-term birth, normal birth weight, and lack of any ASD within first-degree family members (as confirmed through parent interview regarding family medical history). All LR participants had at least one older sibling. Screening for possible ASD in these older siblings was undertaken using the SCQ, with no child scoring above instrument cut-off for ASD (1 score missing). Twenty-nine of the HR children underwent an intervention for another study (Green et al., 2015). To assure that this intervention did not interfere with the results of the current study, intervention status (whether the child took part in the intervention program—treated or control—and also whether they were actually treated) was entered as a between subjects factors. There were no significant effects related to these factors and therefore these results are not mentioned further.

Outcome characterization

Standard measures of cognitive development (Mullen Scales for Early Learning (MSEL); Mullen, 1995) and adaptive development (Vineland Adaptive Behavior Scales; Sparrow, Balla, & Cicchetti, 2005) were collected. The MSEL is a standardized direct developmental assessment that yields a standardized score (mean = 100, SD = 15) of overall intellectual ability (Early Learning Composite, ELC), and subscale T-scores (mean = 50, SD = 10) for receptive language (RL) and expressive language (EL), as well as non-verbal fine motor (FM) and visual reasoning (VR) abilities. The Vineland is a standardized parent-reported interview of everyday adaptive functioning that measures social, communication, daily living and motor skills.

The *Autism Diagnostic Observation Schedule – Second Edition* (ADOS-2; Lord et al., 2012), a standardised interaction observation assessment, was used to assess current symptoms of ASD (114 children were administered Module 2 and 17 children Module 1). Calibrated Severity Scores for Social Affect (SA), Restricted and Repetitive Behaviours (RRB) and Overall Total were computed (Gotham, Pickles, & Lord, 2009; Hus, Gotham, & Lord, 2014), which provide standardized autism severity measures that account for differences in module administered, age and verbal ability. The *Autism Diagnostic Interview – Revised* (ADI-R; Le Couteur, Lord, & Rutter, 2003), a structured parent interview, was completed with parents. Standard algorithm scores were computed for Reciprocal Social Interaction (Social), Communication (Com), and Restricted, Repetitive and Stereotyped Behaviours and Interests (SBRI). These assessments were conducted without blindness to risk-group status by or under the close supervision of clinical researchers (i.e., psychologists, speech therapists) with demonstrated research-level reliability.

The Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1991) was used to assess severity of ADHD symptoms (ADHD t-scores). See Appendix I for relationships between these measures.

As children in this study were 3-years-old, it was possible for a clinical ASD diagnosis to be attained. Experienced clinicians reviewed information on ASD symptomatology (ADOS-2, ADI-R, SCQ), adaptive functioning (Vineland-II), and development (Mullen) for each HR and LR child to ascertain ASD diagnostic outcome according to DSM-5 (American Psychiatric Association, 2013). From the 106 HR participants included in this paper 15 (13 boys, 2 girls) met criteria for ASD (hereafter, HR-ASD). A further 30 participants (19 boys, 11 girls) did not meet ASD criteria, but were neither considered typically-developing, due either to a) scoring above ADI-R cut-off for ASD (Risi et al., 2006) ($n=1$), b) scoring above ADOS-2 cut-off for ASD ($n=12$), c) scoring greater than 1.5 *SD* below the population mean on the Mullen ELC (< 77.5) or on the Mullen EL or RL subscales (< 35) ($n=9$), or meeting both of points *a* or *b* and *c* above ($n=8$). These therefore comprised a HR subgroup presenting other atypicalities (hereafter, HR-Atypical). The remaining 61 participants (28 boys, 33 girls) were typically-developing (hereafter, HR-Typical). None of the 25 LR children met DSM-5 criteria for ASD and none had a community clinical ASD diagnosis.

Multi-target cancellation task

Stimuli

Target and distractor items were chosen from Snodgrass and Vanderwart-like images (Rossion & Pourtois, 2004). For *categorical search*, targets were animals (bears, camels, cats, cows and dogs; one exemplar of each) and distractors were inanimate objects (baskets, barrels, belts, bread and bells; one exemplar of each). For *exemplar*

search, targets were cats (one exemplar) and distractors were inanimate objects (baskets, barrels, belts, bread and bells; one exemplar of each). For *perceptual search*, targets were dogs (one exemplar) and distractors were various chairs and tables that were perceptually similar to the dog exemplar (Figure 2). Stimuli were presented on an Elo AccuTouch 17-in touchscreen monitor with 1280 by 1024 resolution using E-prime.

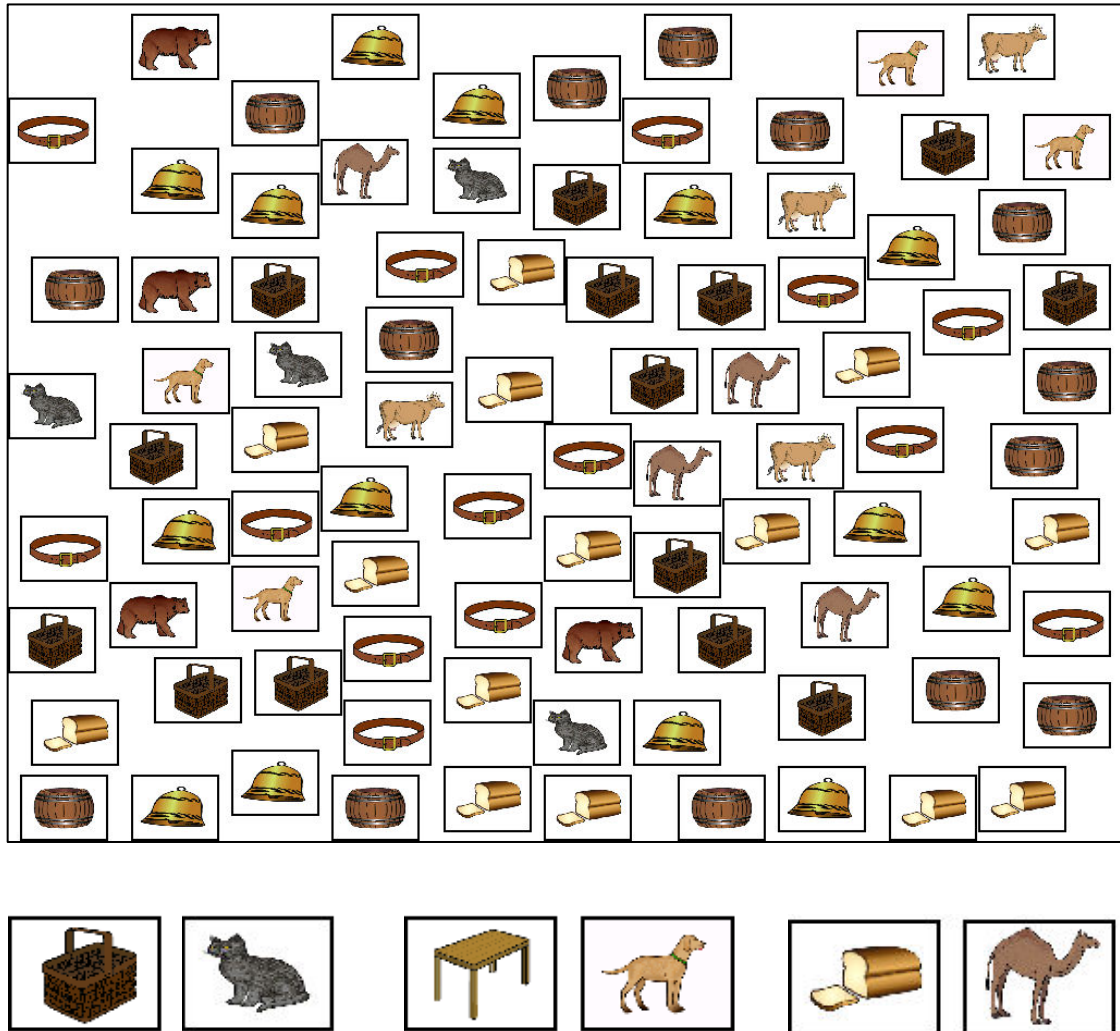


Figure 2. Top: Example trial for categorical search. Bottom: distractor and target examples for exemplar, perceptual, and categorical search. For exemplar and perceptual search, targets were all the same as the target depicted here. Boxes surrounding targets and distractors were 1.25 x 0.94 inches on a 14.94 x 11.94 inch screen.

Procedure

These tasks were adapted from those previously used with children aged 3-6-years old (Steele, Karmiloff-Smith, Cornish, & Scerif, 2012). Children could engage in up to six trials, two of each for categorical, exemplar, and perceptual search. For each trial, participants were presented with a search display on the touch screen. Each display contained 20 target and 70 distractor items in pseudo-random position. Children were asked to search for and touch the a) cats in the exemplar search, b) animals in the categorical search, and c) dogs in the perceptual search. The exemplar and perceptual searches were always run after the categorical search, so as not to bias children to look for specific items (cats/dogs) which would diminish the extent to which the categorical condition tested their category knowledge. The order of condition presentation was the same for all children: 1) conceptual, 2) exemplar, and 3) perceptual. Instructions: “Can you find all the [animals]? When you touch them you'll find a star”. When children successfully touched a target, a star appeared on the screen and remained there for the duration of the trial. When children touched a distractor there was no feedback. There was no time limit for a trial, instead the trial ended when children touched a total of 18 targets or 40 responses were made overall. Children were given neutral reinforcement to keep them engaged—“keep going!” See Table 1 for information of how many children completed at least one trial in each condition.

Table 1

Number of participants who completed at least one trial of each search type by categorical group for entire sample

	LR	HR	HR-Typical	HR-Atypical	HR-ASD
Categorical	24	106	61	30	15
Exemplar	22	94	59	23	12
Perceptual	22	91	56	24	11

LR = low risk, HR = high risk. See below for descriptions of categorical groups

Search measures

To investigate search performance, two sets of measures were analyzed. The first set comprised three traditional measures of search performance: accuracy (number of hits), errors (touches to distractors), and time to completion. These measures were highly skewed and therefore these analyses are included only in Appendix I. Three additional measures produced by CancellationTools were used to investigate general search performance as well as search organization without the difficulty of skew produced by traditional measures. CancellationTools is a free, open source software that aids in both collecting and analyzing cancellation data that reduces human error associated with previous pen and paper task (Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2015). Moreover, it automatically calculates some of the most sensitive measures of search in the literature.

The first measure we used, *Q score*, combines speed and accuracy into a single measure of *search efficiency*, such that Q score equals the number of cancelled targets squared divided by the product of the total number of targets and the total time spent on the task. A high Q score represents a combination of a high number of cancelled targets and high speed of cancellation. This measure was first described by Hills and colleagues (1998) and has since been used in several cancellation studies investigating age and task differences (Byrd, Touradji, Tang, & Manly, 2004; Huang & Wang, 2008).

The second measure, *best R*, is a measure of horizontal or vertical spatial organization and is defined as “the highest absolute value of the Pearson correlation between cancellation rank number and either horizontal or vertical cancellation position” (Dalmaijer et al., 2015). A high best R represents more *spatially systematic search*. This measure has been used to show less spatially systematic search in stroke patients (Brink, Van der Stigchel, Visser-Meily, & Nijboer, 2015; Broeren, Samuelsson,

Stibrant-Sunnerhagen, Blomstrand, & Rydmark, 2007; Mark, Woods, Ball, Roth, & Mennemeier, 2004). Best R has also been used to demonstrate how search becomes more spatially systematic over neurotypical development (Woods et al., 2013). In addition, Woods and colleagues (2013) have shown best R to relate to accuracy in single target search across development (2-17 years) and argue that increased ability to organize search helps sifting through both targets and distractors in traditional visual search tasks.

The third measure, *intersections rate*, quantifies the number of times the search path crosses over itself, divided by the amount of cancellations that are not immediate revisits (Dalmaijer et al., 2015). A high intersections rate reflects *disorganized exploration* (Brink et al., 2015; Rabuffetti et al., 2012; Woods et al., 2013).¹

Longitudinal analysis

In addition to the in depth analysis of search organization in a multi-target cancellation task, the current study investigated concurrent relationships between search organization and social cognition as measured by face recognition. Further, we investigated longitudinal relationships between attention (visual search) and social cognition (face popout) measures at 2-years and the 3-year measures (search cancellation, face recognition) using a cross-lagged path analysis with structural equation modeling (SEM).

2-year-old visual search

¹ Important to note, there are inconsistencies in the literature in how these measures are described. While some describe both best R and intersections rate as measures of “search organization” (Woods et al., 2013), others differentiate them, for example describing best R as “search consistency” and intersections rate as “organization” (Brink et al., 2015). For clarity we use the definitions described in the text.

This task is described in detail in a previous study (Gliga et al., 2015a). Stimuli were arrays of eight letters in a circle on a white background. In each array, all but one letter was the letter “X.” Targets were either a “+,” “V,” “S,” or “O.” There were 32 trials in total: each target in each of the eight locations in the circle. However, due to time constraints only 16 trials were presented. Letters on each trial were red, black, green or blue to add variability (Figure 3). Infants sat on their caregiver’s lap, approximately 60 cm from a Tobii T120 screen. The experiment started only when at least four of the five calibration points were marked as good. Stimuli were presented with TobiiStudio software. Before each trial, the child’s attention was drawn to the center of the screen with an engaging video, and only trials in which the center was fixated within 100 ms of stimulus onset were used for analysis. Each trial was 1500 ms long. The proportion of trials in which children made a first look to the target was used as a measure of search performance. Enhanced performance by the children in the current study has previously been shown to be related to later ASD symptoms and diagnosis (Cheung et al., 2016; Gliga et al., 2015a).



Figure 3. Example stimuli and areas of interest (AOIs) for the 2-year-old visual search task. Taken with permission from (Gliga et al., 2015a)

2-year-old face popout

This task is described in detail in a previous study (de Klerk, Gliga, Charman, Johnson, The BASIS Team, 2013). Stimuli were five color images, one face and four

distractor objects, presented in a circle with a white background (Figure 4). There were 14 trials in total with 7 male and 7 female faces with direct gaze from the MacBrain Face Stimulus Set (Tottenham et al., 2009). Before each trial, a central video was presented to assure children's gaze was at the center of the screen. Each trial lasted 15 seconds and was accompanied by unrelated music. Children sat in their caregiver's lap at approximately 50-55 cm from a Tobii T120 screen. Stimuli were presented using TobiiStudio software. The experiment started only when at least four of the five calibration points were marked as good. The proportion of time children spent looking at the face AOI relative to all target AOIs in the array was used in the current study as a measure of "face engagement." This measure was previously shown to be related to the face recognition task (described below) in a previous cohort of children with high familial risk for ASD (de Klerk et al., 2013).

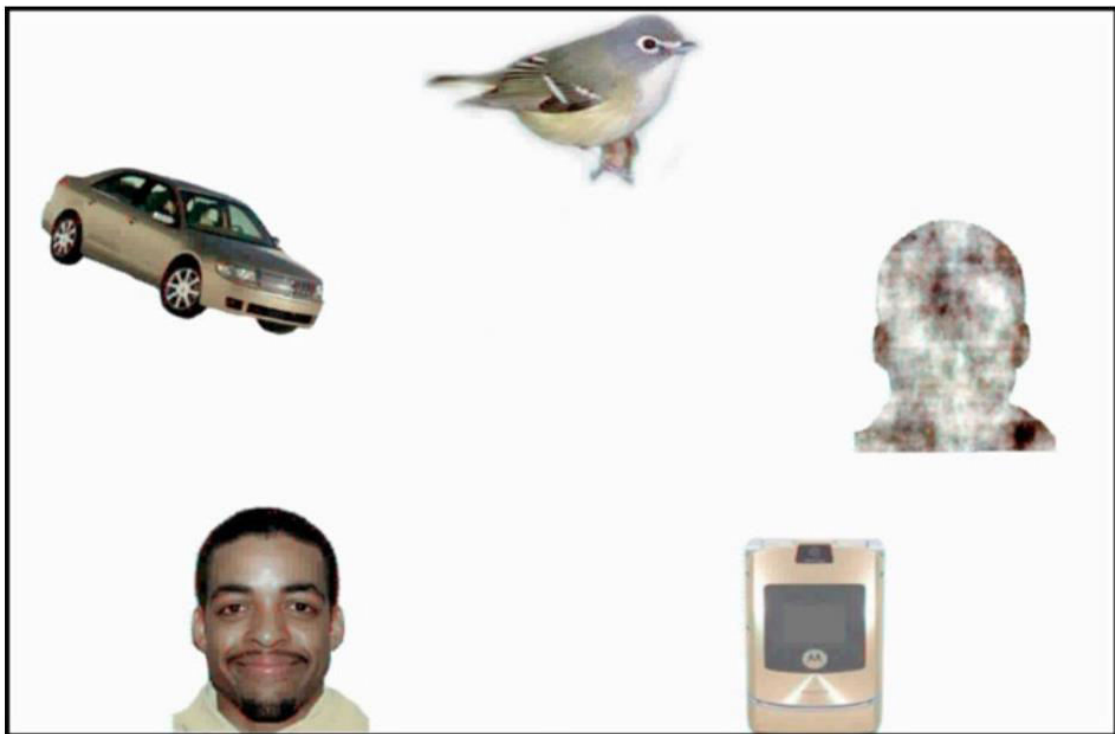


Figure 4. Example stimuli for the 2-year-old face popout task. Taken with permission from (de Klerk et al., 2013).

3-year-old face recognition

This task is described in detail in a previous study (de Klerk et al., 2013). Stimuli were still, black and white images of faces from the MacBrain Face Stimulus Set (Tottenham et al., 2009). In half of the trials, male faces were used as targets and distractors. E-prime software was used to present stimuli and an AccuTouch 17-in touchscreen monitor was used to record responses. During the task children sat on their caregiver's lap or on a chair on their own approximately 50-60 cm from the screen. The procedure consisted of a familiarization and a recognition phase, detailed in Figure 5. There were 16 trials in total, half easy and half difficult. In the easy trials, the target faces presented during familiarization and recognition were identical. In the difficult trials, the facial expression of the target changed from familiarization to recognition, and the distractor face had the same expression as the target during recognition. Accuracy in both easy and difficult trials was used in the current study. In a previous cohort of at risk children, performance on this task was related to earlier face popout, as well as to ASD diagnosis (de Klerk et al., 2013).

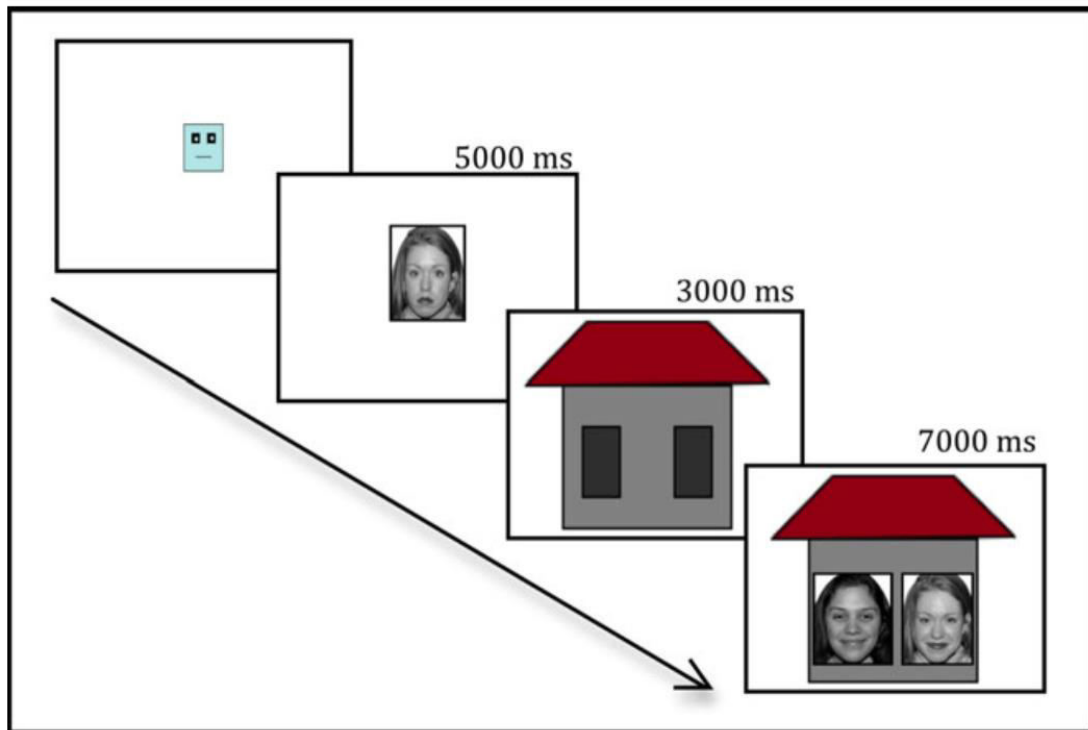


Figure 5. Example stimuli for the 3-year-old face recognition task. Children were presented with a fixation stimulus, followed by the familiarization phase (5000 ms). The familiarization phase was then replaced with an image of a house and the experimenter asked: ‘Where did he/she go? He/she went into the house!’ After 3000 ms, a doorbell sound played and the familiar and novel faces appeared in the house. The experimenter then prompted the child by saying ‘Where did he/she go? Can you find him/her?’ When the child touched the correct face, a smiley appeared on the screen. When the child gave the wrong answer, or did not respond within 7000 ms, no feedback was provided. Taken with permission from (de Klerk et al., 2013).

Statistical approach

Multi-target cancellation task

Two statistical approaches were used. First, in accordance with research domain criteria (RDoC) and a shift away from categorical diagnosis towards continuous characterization of psychopathology (Plomin et al., 2009), we analyzed both ASD and

ADHD symptoms as continuous predictors of search. Second, we investigated ASD diagnostic groups (and continuous ADHD symptoms, as ADHD is not typically diagnosed until later in childhood) as predictors of search.

ASD and ADHD symptoms as predictors of search. To investigate possible relationships with ASD and ADHD symptom severity, Mixed effects models were specified using the *lme4* package in *R* (Bates, Mächler, Bolker, & Walker, 2015). Importantly, this procedure allowed for including children with missing data in one or more conditions. For each dependent measure (Q score, best R, and intersections rate), a model was specified with a fixed effect of condition (exemplar, perceptual, conceptual), MSEL as well as each of the three symptom severity measures (ADOS-SA, ADOS-RRB, CBCL-ADHD) as covariates, a random slope of condition, and a random effect of participant. For these models, *p*-values were determined using the Kenward-Roger approximation for degrees of freedom (Kenward & Roger, 1997) as implemented by the *afex* package in *R* (Singmann, Bolker, & Westfall, 2015). All covariates were centered for these analyses. Although the MSEL and ADOS was completed for all children, the CBCL was not completed for 10 children. These analyses were therefore restricted to the children for whom the CBCL was completed: 23 LR and 98 HR children (see Table 2 for demographics for this limited sample). Although the dependent measures were not skewed, the covariates were slightly skewed; therefore non-parametric statistics were used with follow-up analyses including the covariates. Significance level remained unchanged when removing the 14 children in the sample that received an ASD diagnosis at age 3 (see Appendix I).

Table 2

Participant characteristics, sample limited to those who contributed data to the analyses

Group	Age	Gender (M:F)	MSEL ELC	ADOS-SA	ADOS-RRB	CBCL-ADHD	ADI-Soc	ADI-SBRI	ADI-Com
HR (N=98)	38.84 (1.57)	55:43	103.94** (24.27)	3.45 (3.55)	1.31** (1.43)	55.45*** (7.65)	3.28*** (4.80)	1.46*** (2.48)	3.65*** (4.68)
LR (N=23)	38.52 (2.43)	14:9	118.61 (15.61)	2.83 (3.07)	0.70 (0.82)	51.04 (2.90)	0.91 (1.53)	0.09 (0.29)	0.48 (1.08)

Figures in parentheses are SDs. Mullen Scales for Early Learning, Early Learning Composite (MSEL ELC); Autism Diagnostic Observation Schedule, Social Affect (ADOS-SA); Autism Diagnostic Observation Schedule, Restricted and Repetitive Behaviors (ADOS-RRB); Child Behavior Checklist, ADHD t-scores (CBCL-ADHD); Autism Diagnostic Interview, Social (ADI-Soc); Autism Diagnostic Interview, Restricted, Repetitive and Stereotyped Behaviours and Interests (SBRI), and Autism Diagnostic Interview, Communication (ADI-Com) (see above for measure characterization). Significant differences between the HR and LR groups indicated by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

ASD diagnostic outcome as a predictor of search. To investigate possible relationships with ASD diagnostic outcome, mixed effects models were specified with condition (exemplar, perceptual, categorical) and diagnostic group (LR, HR-Typical, HR-Atypical, HR-ASD) as fixed effects, MSEL and CBCL-ADHD as covariates, a random slope of condition, and a random effect of participant for all three dependent measures (Q score, best R, and intersections rate). All covariates were centered for these analyses. As mentioned above, not every child had a complete CBCL. Of those did there were 14 in the ASD group, 28 were HR-atypical, and 56 were HR-typical (23 in the LR group), and these are the children contributing to the analyses below.

Structural equation modeling (SEM) for longitudinal data

SEMs were specified using the *lavaan* package in *R* (Rosseel, 2012). The maximum likelihood estimation with robust (Huber-White) standard and a scaled test statistic that is (asymptotically) equal to the Yuan-Bentler test statistic was used in order to account for potentially non-normally distributed data. Participants with missing data were deleted list-wise, which resulted in 84 children included: 16 LR and 68 HR. Model fit was assessed using the χ^2 of model fit as well as the comparative fit index (CFI) and Tucker-Lewis index (TFI). The χ^2 test is an absolute fit statistic, representing the difference between the unrestricted covariance matrix (the observed data) and the restricted covariance matrix (the model). If the test is *not* significant, then the evidence is against rejecting the null hypothesis, which is that there is no difference between the restricted and unrestricted covariance matrices. In sum, the *larger* the *p* value, the better the fit between the data and the model. The CFI ranges from 0-1, with a value over 0.9 representing a good model fit as a rule of thumb, and adjusts for issues of sample size that occur when using the χ^2 test. The TFI typically ranges from 0-1 (although larger

values are possible), with a value over 0.95 indicating a good model fit as a rule of thumb.

Results

Multi-target cancellation task

ASD and ADHD symptoms as predictors of search

For **Q score**, our index of overall search efficiency, there was a significant effect of condition, $F(2, 99.67) = 95.64, p < 0.001$. This effect was driven by Bonferroni-corrected significant differences among conditions (all $p < 0.001$), with exemplar search yielding the highest Q score, perceptual search with the next highest and categorical search with the lowest (see Table 3 for descriptives). There was also a significant effect of MSEL, $F(1, 113.80) = 30.04, p < 0.001$, with higher developmental ability related to higher Q scores (greater speed and accuracy). Because manual responses were required to estimate performance, we were concerned this effect may reflect differences in fine motor skills. However, this does not seem to be the case since both the fine motor, $F(1, 112.30) = 21.10, p < 0.001$, and the visual reception scales, $F(1, 114.87) = 20.49, p < 0.001$, related to performance. In addition, we were concerned that perhaps differences in performance were associated with language skills. When including the expressive language, $F(1, 112.54) = 15.18, p < 0.001$, and receptive language, $F(1, 114.03) = 24.05, p < 0.001$, scales separately instead of the ELC they were significant covariates, however including them did not affect the other results. There was a condition by ADOS-SA interaction, $F(2, 108.37) = 3.69, p = 0.03$. Following up this interaction with non-parametric Spearman's Rho correlations using the full sample for each condition revealed a significant negative correlation between ADOS-SA and Q score in the categorical search condition, $r(120) = -0.20, p = 0.025$, with higher ASD symptoms

related to low Q score (less efficient search), but no significant correlations in the other two conditions ($p > 0.250$).

Table 3
Measures of search quality and organization across conditions

Measure	Condition		
	Categorical	Exemplar	Perceptual
Q score	0.27(0.15)	0.51(0.19)	0.43(0.17)
Best R	0.48(0.15)	0.56(0.16)	0.53(0.15)
Intersections rate	0.28(0.22)	0.17(0.12)	0.18(0.12)

Figures in parentheses are SDs. Sample limited to those children who contributed data to the analyses.

For **best R**, our index of spatial systematicity, there was a significant effect of condition, $F(2, 102.57) = 6.97$, $p = 0.001$. This effect was driven by Bonferroni-corrected significantly lower best R for categorical search compared to exemplar search ($p < 0.001$), and perceptual search ($p = 0.024$), but no significant difference between perceptual and exemplar search ($p > 0.250$) (see Table 3). There was also a significant effect of CBCL-ADHD, $F(1, 112.68) = 7.42$, $p = 0.007$, with higher ADHD symptom severity related to lower best R (more spatially unsystematic search). Q score and best R did not relate to each other (see Appendix I). Moreover, including the expressive language and receptive language scales did not affect the results and were not significant covariates when used instead of the ELC.

For **intersections rate**, our index of spatial organization, there was a significant effect of condition, $F(2, 104.48) = 15.14$, $p < 0.001$. This was driven by Bonferroni-corrected significantly higher intersections rate for categorical search compared to perceptual search ($p < 0.001$) and exemplar search ($p < 0.001$), but no difference between perceptual and exemplar search ($p > 0.250$) (see Table 3). There were also significant effects of three of the covariates: ADOS-SA, $F(1, 123.35) = 5.21$, $p = 0.02$, ADOS-RRB, $F(1, 113.29) = 5.33$, $p = 0.02$, CBCL-ADHD, $F(1, 114.97) = 11.58$, $p <$

0.001, with higher scores on the ADOS-SA, ADOS-RRB and CBCL-ADHD related to higher intersections rates (i.e., more disorganized search). There was also a marginally significant effect of MSEL, $F(1, 115.02) = 3.40, p = 0.07$, with lower scores on the ELC related to higher intersections rates (i.e., more disorganized search). Again, including the fine motor, visual reception, expressive language, and receptive language sub-scales did not affect the results. The main effect of ADOS-RRB was further qualified by an ADOS-RRB-by-condition interaction, $F(2, 106.62) = 4.44, p = 0.01$. To follow up this interaction, non-parametric Spearman's Rho correlations using the full sample were run for each condition, revealing a significant positive relationship between ADOS-RRB and intersections rate in the perceptual condition only, $r(104) = 0.21, p = 0.036$, suggesting that the more severe restricted interests and repetitive behaviors were, the least organized search was, but no significant correlations in the other two conditions ($p > 0.250$). Intersection rate negatively correlated with Q score overall, with more disorganized search related with poorer search performance (see Appendix I for details).

In light of the main effects of CBCL-ADHD and ADOS-SA without further interactions with condition (i.e. ADOS-RRB interacted with condition), another model was run in order to determine if the main effects were further qualified by an interaction between the symptoms. The main effects remained, but the interaction term was not significant ($p > 0.250$), which is compatible with independent contribution from ASD and ADHD symptoms.

ASD diagnostic outcome as a predictor of search

In addition to using continuous measures of ASD symptoms as predictors, we investigated ASD diagnostic outcome as a fixed effect. However, these analyses are prefaced by caution, given limited statistical power and uneven Ns (only 14 in the HR-

ASD group and at the highest 56 in the HR-Typical group). In addition, as seen in Table 2, there were significant differences in covariates between HR and LR groups, which makes including a between-subjects effect inappropriate due to the statistical assumptions of covariate analyses. This is likely to be exacerbated when using diagnostic group, further adding to our caution. Here we report inferential statistics for readers interested in pursuing replication with a larger sample, but we will focus on the continuous symptom analyses for our discussion. See Table 4 for descriptives.

For **Q Score**, there was an effect of condition, $F(2, 101.01) = 63.19, p < 0.001$, and MSEL, $F(1, 113.97) = 20.57, p < 0.001$ (in the same direction as above in continuous analyses).

For **Best R**, there was an effect of condition, $F(2, 103.79) = 6.17, p = 0.003$ and CBCL-ADHD, $F(1, 111.89) = 7.17, p = 0.009$ (in the same direction as above in continuous analyses).

For **intersections rate**, there was an effect of condition, $F(2, 105.64) = 13.81, p < 0.001$, and CBCL-ADHD, $F(1, 114.32) = 4.98, p = 0.03$ (in the same direction as above in continuous analyses).

Table 4

Descriptive statistics for participant characteristics and dependent measures split by diagnostic group

Diagnosis	Age	MSEL ELC	ADOS-SA	ADOS-RRB	CBCL-ADHD	ADI-Soc	ADI-SBRI	Q score				Best R				Intersections rate			
								E	P	C	E	P	C	E	P	C	E	P	C
LR	38.4	119.48	2.88	0.8	51.04	0.96	0.08	0.52	0.46	0.33	0.6	0.56	0.5	0.12	0.14	0.12	0.14	0.2	0.2
	2.38	15.27	3.03	0.91	2.9	1.49	0.28	0.13	0.19	0.14	0.18	0.15	0.15	0.12	0.09	0.12	0.12	0.09	0.15
	25	25	25	25	23	25	25	22	22	24	22	22	24	22	22	24	22	22	24
HR-Typical	38.92	114.57	1.64	0.75	53.2	1.43	0.4	0.58	0.48	0.31	0.55	0.54	0.47	0.17	0.17	0.17	0.17	0.17	0.28
	1.48	15.79	1.27	0.91	5.65	2.04	0.85	0.18	0.19	0.13	0.15	0.16	0.14	0.11	0.1	0.11	0.11	0.1	0.2
	61	61	61	61	56	60	60	59	56	61	59	56	61	59	56	61	59	56	61
HR-Atypical	38.73	89	5.93	1.97	56	2.64	1.29	0.46	0.39	0.17	0.6	0.51	0.5	0.16	0.2	0.16	0.16	0.2	0.25
	1.86	25.38	3.58	1.71	7.56	2.78	2.29	0.22	0.15	0.12	0.16	0.15	0.16	0.12	0.14	0.16	0.12	0.14	0.23
	30	30	30	30	28	28	28	23	24	30	23	24	30	23	24	30	23	24	30
HR-ASD	38.73	87.2	5.6	2.07	63.36	12.13	5.87	0.33	0.38	0.18	0.51	0.51	0.47	0.21	0.23	0.47	0.21	0.23	0.37
	1.62	27.47	5.11	1.49	9.68	5.96	2.45	0.17	0.15	0.14	0.19	0.12	0.16	0.14	0.15	0.16	0.14	0.15	0.29
	15	15	15	15	14	15	15	12	11	15	12	11	15	12	11	15	12	11	15

E = exemplar search, P = perceptual search, and C = categorical search. Mullen Scales for Early Learning, Early Learning Composite (MSEL ELC); Autism Diagnostic Observation Schedule, Social Affect (ADOS-SA); Autism Diagnostic Observation Schedule, Restricted and Repetitive Behaviors (ADOS-RRB); Child Behavior Checklist, ADHD t-scores (CBCL-ADHD); Autism Diagnostic Interview, Social (ADI-Soc); and Autism Diagnostic Interview, Restricted, Repetitive and Stereotyped Behaviours and Interests (SBRI). Age is provided in months. Means are in bold above standard deviations and sample sizes.

Longitudinal analyses

First, non-parametric correlations (Spearman's Rho) were run to investigate potential relationships between all longitudinal measures, including all participants (see Table 5 for descriptive statistics). Although the 3-year-old cancellation measures were highly correlated with each other, only Q score for conceptual search correlated positively with the 3-year-old face recognition task (better search efficiency associated with better face recognition). Additionally, the 3-year-old cancellation measures did not correlate with the 2-year-old face popout performance, and only best R in conceptual search correlated negatively with the 2-year-old visual search performance (better single target visual search [2-years] associated with more disorganized multi-target search [3-years]). Finally, 2-year-old visual search correlated negatively with 3-year-old face recognition performance (better single target visual search [2-years] associated with poorer face recognition [3-years]), although only for the full sample (Table 6, Table 7).

Table 5
Longitudinal data descriptive statistics

	Full sample				Sample included in SEM			
	<u>2-years-old</u>		<u>3-years-old</u>		<u>2-years-old</u>		<u>3-years-old</u>	
	VS	FP	FR (easy)	FR (difficult)	VS	FP	FR (easy)	FR (difficult)
Mean	0.27	0.31	0.61	0.61	0.28	0.32	0.61	0.64
STD	0.19	0.14	0.22	0.2	0.2	0.15	0.22	0.19
N	120	113	122	122	84	84	84	84

VS = visual search, FP = face popout, FR = face recognition. Measure for visual search is proportion of trials with first looks to target. Measure for face popout is proportion of time spent viewing face AOI. Measure for face recognition is accuracy.

Table 6

Spearman's Rho correlation table for 2- and 3-year-old attention and social cognition measures, full sample

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. 3yo Q score (conceptual)	1	.595** 130	.475** 112	0.081 130	0.008 115	.200* 112	-.239** 130	-.350** 115	-.09 112	0.145 121	.203* 121	-0.138 113	-0.052 119
2. 3yo Q score (exemplar)		1	.571** 106	-0.033 115	0.007 116	0.116 106	-0.018 115	-.418** 116	-0.177 106	0.176 109	0.008 109	-0.165 101	0.02 106
3. 3yo Q score (perceptual)			1	-0.026 112	-0.005 106	0.146 113	0.056 112	-.215* 106	-.359** 113	0.178 107	-0.001 107	-0.104 99	-0.058 104
4. 3yo best R (conceptual)				1	0.107 115	0.148 112	-.381** 130	-0.098 115	-0.043 112	-0.083 121	0.007 121	0.034 113	-.191* 119
5. 3yo best R (exemplar)					1	0.143 106	0.041 115	-.334** 116	-.264** 106	-0.184 109	0.071 109	-0.071 101	-0.013 106
6. 3yo best R (perceptual)						1	-0.152 112	-0.19 106	-.383** 113	-0.103 107	0.061 107	-0.091 99	-0.152 104
7. 3yo intersections rate (conceptual)							1	0.177 115	0.148 112	0.1 121	0.049 121	-0.024 113	-0.002 119
8. 3yo intersections rate (exemplar)								1	.240* 106	-0.13 109	-0.072 109	0.143 101	0.076 106
9. 3yo intersections rate (perceptual)									1	-0.011 107	-0.027 107	0.132 99	0.05 104
10. 3yo face recognition (accuracy, easy)										1	.196* 122	0.002 107	-.198* 111
11. 3yo face recognition (accuracy, difficult)											1	0.089 107	-0.056 111
12. 2yo face popout (prop of time looking to face)												1	-0.054 111
13. 2yo visual search (prop first look to target)													1 120

Table 7
Spearman's Rho correlation table for 2- and 3-year-old attention and social cognition measures, sample used for SEM

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. 3yo Q score (conceptual)	1	.566**	.460**	0.178	0.054	0.153	-.373**	-.339**	0.028	0.164	.254*	-0.14	-0.021
2. 3yo Q score (exemplar)		1	.584**	0.047	-0.025	0.15	-0.034	-.449**	-0.106	0.209	0.026	-0.117	0.016
3. 3yo Q score (perceptual)			1	-0.05	-0.085	0.148	0.104	-0.193	-.263*	0.16	0.005	-0.146	-0.009
4. 3yo best R (conceptual)				1	0.076	0.158	-.385**	-0.158	-0.032	-0.103	-0.027	0.036	-.217*
5. 3yo best R (exemplar)					1	0.183	0.058	-.403**	-.233*	-0.177	-0.022	-0.144	0.015
6. 3yo best R (perceptual)						1	-0.083	-0.159	-.379**	-0.122	0.127	-0.066	-0.116
7. 3yo intersections rate (conceptual)							1	0.163	0.046	0.051	-0.073	-0.119	0.011
8. 3yo intersections rate (exemplar)								1	0.142	-0.044	-0.063	0.127	0.095
9. 3yo intersections rate (perceptual)									1	0.004	-0.009	0.138	0.046
10. 3yo face recognition (accuracy, easy)										1	0.138	-0.027	-0.19
11. 3yo face recognition (accuracy, difficult)											1	0.051	-0.039
12. 2yo face popout (prop of time looking to face)												1	-0.036
13. 2yo visual search (prop first look to target)													1

When including all 3-year-old cancellation measures into a “cancellation” latent variable (nine measures: Q score, best R and intersections rate for perceptual, conceptual and exemplar search) and including 3-year-old face recognition accuracy for both easy and difficult trials into a “face recognition” latent variable, the model fit was very poor ($\chi^2(61) = 139.52$, $p < 0.001$, comparative fit index [CFI] = 0.50, Tucker-Lewis index [TLI] = 0.37). For this reason, three separate models were run instead: Q score, best R and intersections rate for all three conditions were entered into the latent 3-year-old “cancellation” variable separately. Q score, best R and intersections rate models demonstrated similar results, therefore the best fitting model (using intersections rate) is shown here (Figure 6, model fit: $\chi^2(10) = 6.24$, $p = 0.80$, comparative fit index [CFI] = 1.00, Tucker-Lewis index [TLI] = 10.44). These results were also the same as when including all nine measures into a “cancellation” latent model, despite the poor fit.

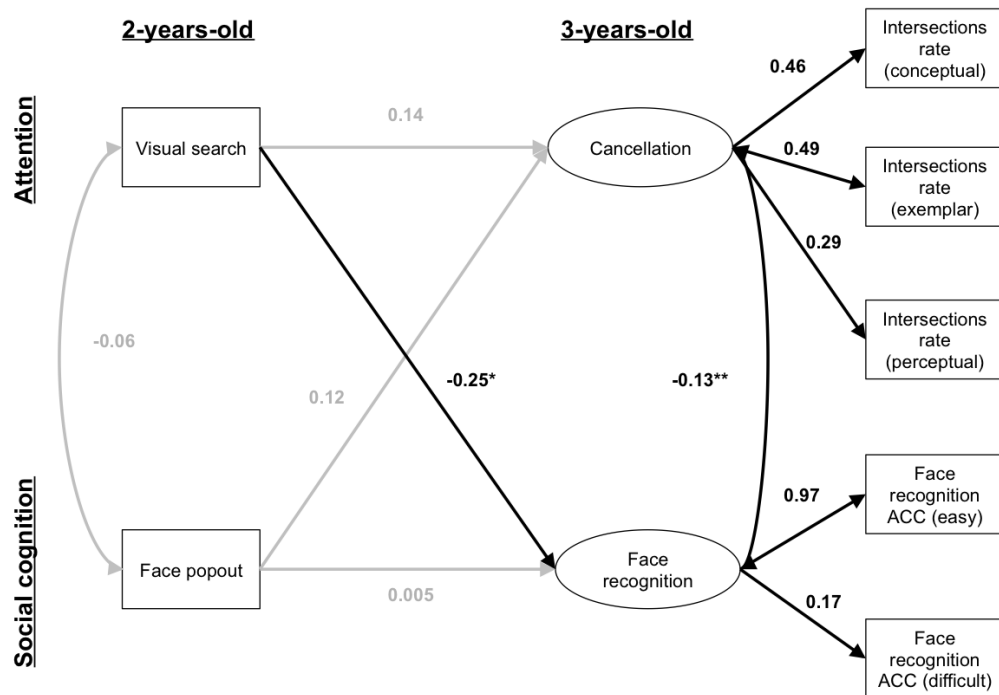


Figure 6. Cross-lagged SEM path analysis including social cognition and attention measures at 2- and 3-years-old. Dark paths were significant, numbers next to paths represent the standardized regression coefficients. Paths marked with ‘*’ had *p* values less than 0.05, and ‘**’ less than 0.01. ACC = accuracy.

Discussion

The current study utilized a multi-target visual search cancellation task with naturalistic objects as targets and distractors in a sample of 3-year-old children with an older sibling with ASD—a population that presents high ASD and ADHD symptoms. The study sought to answer the question: do ASD symptoms and/or an ASD diagnosis, as well as ADHD symptoms, relate to search efficiency, systematicity and organization in varying search conditions? More specifically, does poor performance in categorical search, where targets represent a category (animals), and enhanced performance in perceptual search, where targets are perceptually similar to distractors, relate to high

ASD symptom severity and/or an ASD diagnosis, consistent with previous literature? In addition, how do co-occurring ADHD symptoms relate to search performance?

Both ASD and ADHD symptoms related to search performance, but not always in the direction hypothesized given the prior literature. First, a measure of ASD symptoms, the ADOS-SA, related to search efficiency in the categorical search condition specifically, with lower speed/accuracy (Q score), i.e., lower efficiency, associated with high ADOS-SA scores. This confirmed our hypothesis based on the literature on fully diagnosed cases of ASD suggesting difficulties with categorical knowledge (Naigles et al., 2013). Although the specific mechanism behind this impairment could not be determined by the current study, some researchers argue that, in ASD, impaired categorical knowledge depends on a relative enhanced ability to determine how things are different and a difficulty determining how things are the same (Soulières, Mottron, Giguère, & Larochelle, 2011; Soulières, Mottron, Saumier, & Larochelle, 2006). Although one might expect that difficulty with categories might lead children at risk to adopt a strategy in which they search for each basic level of the category sequentially, ASD symptom severity did not relate to more frequent use of this strategy (Appendix I).

ASD symptoms did not relate to better search efficiency in the perceptual search condition, contrary to our original hypothesis derived from fully diagnosed ASD. A significant literature suggests that individuals with ASD (e.g., Plaisted et al., 1998) as well as those not diagnosed with ASD but with high autism traits (Brock et al., 2011) perform better in difficult visual search conditions when targets and distractors are perceptually similar. Researchers have argued this is due to an enhanced perceptual ability to discriminate features (Joseph et al., 2009; Kaldy et al., 2016; O'Riordan & Plaisted, 2001; Swettenham et al., 2012). However, we did not replicate these findings

when using multi-target cancellation with more realistic target and distractor objects and investigating ASD symptom severity in a sample of young children at risk for high ASD symptoms. Indeed, high ADOS-RRB was associated with greater *disorganization* (intersections rate) in the perceptual condition in particular. Importantly, these results are robust to controlling for overall developmental ability (Mullen scores) and are therefore not the result of low ability in this sample. This is, however, consistent with one of the few studies investigating realistic object visual search in ASD. Riby and colleagues (2012) found that children with ASD had worse performance when asked to search for a butterfly image among distracting objects. Perhaps, when faced with the multitude of features present in more realistic search objects, an enhanced ability to discriminate particular features is no longer helpful. Indeed, this dilemma makes developing computational models that predict eye-movements towards complex targets difficult, and is an active area of research (e.g., Zelinsky, Adeli, Peng, & Samaras, 2013). Alternatively, it is possible that perceptual superiority is specific to particular features, such as line orientation (Dickinson, Jones, & Milne, 2014), or to the identification of single items within the search field, but the advantage dissipates when exemplars have to be sequentially found.

Second, ADHD symptoms, but not ADOS-SA scores related to search systematicity (best R), with poorer systematicity associated with higher ADHD symptoms across all three conditions. Although the lack of a relationship with ASD symptoms may appear surprising given Pellicano and colleagues' (2011) finding of poorer systematicity by children with ASD in their foraging task, this may be due to task differences. Pellicano and colleagues (2011) measured systematicity as consistent search *across* trials with regards to statistical regularities present in the overall task, which they argue relates to inferring and capitalizing on rules, whereas here we measured

systematicity in spatial search pattern within trials separately. We believe this to be more indicative of planning than rule use, as there were no similar rules to be inferred in the current task. In addition, the relationship with ADHD confirms our initial hypotheses based on the previous literature of both large and small scale search (Mullane & Klein, 2008; Rosetti et al., 2016).

Third, for search organization (intersections rate), high ADOS-SA and ADHD scores both contributed to more disorganized search. Thus, in this sample, the relationship between ASD symptoms and disorganized search was not explained by ADHD symptoms alone, but rather levels of both symptoms contributed independently to poor search organization. This finding is relevant to the literature investigating comorbid ASD and ADHD that has developed over the past decade. Some hypothesize that, even within a single domain such as attention, ASD and ADHD are associated with different types of impairments such that comorbid ASD and ADHD will demonstrate both sets of impairments (e.g., Tye et al., 2014), or sometimes, when ASD and ADHD associate with opposite attention patterns, to a cancelling out of effects (Gliga, Smith, Likely, Charman, & Johnson, 2015b). Yet another perspective suggests that attentional impairment only occurs with the presence of ADHD, either in “pure” cases or comorbid ASD and ADHD (Sinzig, Bruning, Morsch, & Lehmkuhl, 2008; van der Meer et al., 2014). Our results instead suggest that ASD and ADHD symptoms contribute independently to exacerbate the same attentional impairment (Yerys et al., 2009).

Interestingly, although both ASD and ADHD symptoms were related to poorer search organization in general across conditions, ADHD symptoms did not relate to poor search efficiency and ASD symptoms only related to poor search efficiency in categorical search. This was despite the fact that more organized search (lower intersections rate) was generally associated with better search efficiency (higher Q

score) (see Appendix I). The lack of a relationship between search organization and search efficiency in the context of ASD and ADHD symptoms is interesting as it suggests that rather than indexing an “impairment,” these measures point to the existence of compensatory strategies that allow certain individuals to succeed in the search task despite adopting atypical foraging strategies.

Aside from ASD and ADHD symptoms, for all three measures of search performance and organization, categorical search in general proved more difficult than exemplar search as we hypothesized. This is consistent with the recent literature investigating categorical search with single targets and realistic target and distractor objects (Maxfield & Zelinsky, 2012; Schmidt & Zelinsky, 2009) and extends this finding to multi-target search cancellation as well as, for the first time, to a very young population of children. Although this may be due to difficulty with category knowledge, particularly given the young age of participants, previous literature has shown similar difficulty in adults in single target visual search (Maxfield & Zelinsky, 2012; Schmidt & Zelinsky, 2009). Without comparison to adults and/or testing category knowledge in this young population in addition to the cancellation task, it is difficult to determine if performance in this task related to category knowledge specifically. It is also possible that poorer performance in categorical search is due to the lack of perceptual specificity that helps to guide visual search to realistic, complex objects, or the tendency to combine instances of a category into a prototype that may have little overlap with specific search target exemplars, as has been suggested previously (Hout & Goldinger, 2015; H. Yang & Zelinsky, 2009; Zhang et al., 2006)

In addition, for Q score, perceptual search proved more difficult than exemplar search, again as we hypothesized. This increased difficulty is consistent with the vast single target search literature using simple targets and distractors (Duncan &

Humphreys, 1989; Treisman, 1991) as well as single target search using more realistic objects (R. G. Alexander & Zelinsky, 2011), and again extends this finding to multi-target search cancellation as well as to a very young population.

Finally, longitudinal analysis using structural equation modeling (SEM) revealed a concurrent relationship between search cancellation performance and face recognition performance at 3-years, which has previously been shown to relate to familial risk for ASD (de Klerk et al., 2013). However, single target visual search at 2-years did not predict performance on the 3-year search cancellation task and face popout at 2-years did not predict face recognition performance at 3-years, as we had expected. Instead, most relevant to the current thesis, there was a unidirectional relationship, with visual search at 2-years (an index of non-social attention, see below for caveats) predicting face recognition at 3-years (an index of social cognition). This is the first time, to our knowledge, that longitudinal relationships across multiple social cognition and attention measures have been investigated in young children at familial risk for ASD, and this finding is suggestive of a primary impairment of attention that has been suggested previously in the literature (Keehn et al., 2013).

There are, however, several limitations to this analysis. Ideally the attention and social cognition measures would be the same at multiple timepoints, in order to measure change in a unitary construct, which was not the case in the current study. Even more problematically, the lack of relationships across measures within the “attention” and “social cognition” constructs over time in the model addressed here demonstrate that lack of unity, and suggest caution when interpreting the results. A lack of a relationship between visual search at 2-years and search cancellation at 3-years may suggest that single target search and multi-target search do not index overall better selection skills. Importantly, it may be the case that while more traditional, single-target visual search

tasks are thought to index selective attention, which has been argued to be a mechanism through which autistic individuals demonstrate enhanced search capacity (Kaldy et al., 2016; Keehn et al., 2013), the current multi-target cancellation task may index more traditional executive function skills, such as planning. As discussed in Chapter 1, executive functions are thought to be impaired in ASD, and this may explain the relationship between high ASD symptoms and more disorganized search, highlighting the difficulty in separating atypical attention and executive function accounts of ASD.

In addition, although previous research has shown a relationship between face popout at 8-months and face recognition at 3-years (de Klerk et al., 2013), we did not demonstrate a similar relationship with face popout at 2-years. Perhaps the stimuli are not as engaging for 2-year-olds as they are for 8-month olds, and different stimuli should be used for this age group to measure face engagement.

In conclusion, our study suggests that the search superiority thus far associated with ASD symptoms may only be evident under restricted experimental conditions, including single target search with targets/distractors distinguished by few visual features. In our multi-target cancellation task with more complex targets/distractors, ASD symptoms were associated with more disorganized search across conditions, and poorer search performance for categorical search in particular. In addition, ADHD symptoms contributed to search disorganization, which further reinforces the research domain criteria call to investigate multi-dimensional contributions to cognitive profiles. Importantly, the unidirectional longitudinal relationship whereby non-social selective attention predicts social cognition over time, but not the reverse, provides preliminary evidence in support of the hypotheses posed in this thesis: that non-social attention contributes to the social impairments in ASD, however important caveats are noted.

Chapter 3: Disentangling autism spectrum and attention-deficit/hyperactivity symptoms over development in fragile X syndrome

*Portions of this chapter appear in an in press review paper: **Doherty, B., & Scerif, G. (in press).** Genetic syndromes and developmental risk for autism spectrum and attention deficit/hyperactivity disorders: Insights from fragile X syndrome. *Child Development Perspectives*.*

Candidate contribution: The candidate was not involved in the design of these experiments, nor in the recruitment of participants/collection of data at any timepoint. The candidate contributed to this study by: creating a novel analysis strategy, implementing data analysis, and writing up the report. Ethical approval in addition to that granted to the cohort study as a whole (below) was sought through the University of Oxford Medical Sciences Division Interdivisional Research Ethics Committee.

Introduction

Although in Chapter 2 we investigated both autism spectrum disorder (ASD) symptoms and attention deficit/hyperactivity (ADHD) symptoms in young children with an older sibling diagnosed with ASD, this population was not ideal for investigating both ASD and ADHD symptoms together in their own right. While these children were at high familial risk for ASD, there is no precedence in the literature for considering these children to be at high risk for ADHD because of an older ASD sibling. Chapter 2 therefore examined ADHD symptoms in these children only as a potential (confounding) source of variation in visual search performance as opposed to a core

feature of that sample. The current study sought to investigate ASD and ADHD symptoms in their own right by examining the relationship between them over time in a population at high risk for both—children with fragile X syndrome (FXS). Importantly, this allowed for examining the relationship between social functioning and atypical attention at the symptoms level (ASD and ADHD symptoms respectively), in compliment to the previous chapter that investigated the cognitive level.

Fragile X syndrome is the most common known cause of genetically inherited intellectual disability, with recent prevalence estimates of 1 in 2,500 in both males and females (P. J. Hagerman, 2008). The disorder results from a mutation on the *FMR1* gene that leads to a reduction of the fragile X mental retardation protein, FMRP. There are marked sex differences in the presentation of the FXS phenotype: *FMR1* is located on the X chromosome, and females, for whom one of the two X chromosomes is randomly inactivated, have more variable and overall less severe impairment than males (Grigsby, Kemper, Hagerman, & Myers, 1990).

At the cellular level, FXS has been consistently associated with anatomical and functional changes related to the synaptic connections between neurons (see Santoro, Bray, & Warren, 2012 for an in-depth review). Interestingly, mouse models of FXS suggest that these changes may be transient and occur only at specific timepoints in development (Meredith, 2015), stressing the importance of a developmental perspective. These temporal dynamics, combined with differing timings of environmental influences, may explain variation in the cognitive and psychiatric outcomes often seen in the literature (e.g., Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012).

Multiple cognitive symptoms characterize FXS: significant attentional, memory, and sociocognitive deficits above and beyond levels that would be predicted given overall developmental delay. Subtle behavioral and cognitive delays are evident as early

as infancy, with parents becoming concerned about their children on average as early as 11.6 months of age, although clinical confirmation of a first diagnosed case in a family is often later (D. B. Bailey, Raspa, Bishop, & Holiday, 2009). Diagnosis for younger siblings of children with FXS can then come earlier, even prenatally. In addition to these early concerning signs, from infancy FXS presents with a distinct cognitive profile: poor response inhibition (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2007), poor saccadic eye-movement control (Scerif et al., 2005), and prolonged visual attention to objects, i.e. sticky fixation (Roberts, Hatton, Long, Anello, & Colombo, 2012). Later in development, school children and adolescents also display poor response inhibition (K. Sullivan et al., 2007) and atypical patterns of visual attention, including distinctive impairments in selective, sustained and divided attention (Hooper, Hatton, & Baranek, 2000; Munir, Cornish, & Wilding, 2000a). Finally, executive function is clearly affected in FXS in childhood, with concomitant working memory impairments (Lanfranchi, Cornoldi, Drigo, & Vianello, 2009), despite relative strengths in long-term memory and daily living skills (Hatton et al., 2003).

In addition to these cross-sectional profiles, vital insights have come from studying FXS longitudinally. For example, a combined cross-sectional and prospective longitudinal design examined early profiles of attention and working memory impairment in FXS (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013). The cross-sectional data suggested difficulties with no definitive improvement appearing over chronological age. In contrast, when investigating the same weaknesses in a longitudinal manner, boys with FXS improved over time. This discrepancy demonstrates the power of longitudinal designs. Indeed, these longitudinal developmental improvements in inhibitory control have since been measured in very young children with FXS—as young as three-years-old (Tonnsen, Grefer, Hatton, &

Roberts, 2014). For these reasons, as well as to investigate a more causal hypothesis about the role of atypical attention (ADHD symptoms) in social functioning (ASD symptoms) at the symptoms level, the current study employed a longitudinal design.

Importantly for the current study, FXS serves as a model for behaviorally defined disorders for which individuals with FXS are at high risk, including ASD and ADHD. With regards to ASD, approximately 33-67% of FXS patients meet the clinical diagnosis (Clifford et al., 2007; Rogers, Wehner, & Hagerman, 2001). The risk is even higher for ADHD: approximately 74% of individuals with FXS meet the criteria for a clinical ADHD diagnosis (Backes et al., 2000). Despite the high risk for these behaviorally defined disorders, as noted above, variability in behavioral outcomes across individuals with FXS is the rule. Therefore investigating what factors cause individual differences in ASD and ADHD symptoms is of both theoretical and clinical importance. Why do many children with FXS present with social and cognitive control problems similar to those experienced by children diagnosed with ASD and ADHD, while others do not? One advantage of using FXS as a model for behaviorally defined disorders arises from the substantially earlier diagnosis; FXS can be diagnosed as early as pre- or perinatally (when an older sibling has already been diagnosed), whereas ASD is diagnosed at age 3 on average (Fountain, King, & Bearman, 2011) and ADHD around age 7 (Visser et al., 2014), making FXS an ideal model for assessing high risk in early development.

Several longitudinal studies have investigated what predicts variability in ASD symptoms in children with FXS. For example, visual, auditory, and multimodal attention were measured in young boys with FXS, aged between 4 and 10 years of age at time one and again 12 months later. At an individual level, while visual attention was a significant longitudinal predictor of ADHD symptoms in the boys with FXS (Scerif et

al., 2012), auditory attention predicted later symptoms related to ASD (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012). Similarly, attention skills in infants with fragile X syndrome assessed at 9, 12, and 18 months related to ASD symptoms (Roberts et al., 2012). Other work reports that the greatest predictor of ASD symptoms in FXS is not overall cognitive delay or IQ, but rather adaptive socialization (Hernandez et al., 2009). However, a central point for debate in investigating FXS as a model for ASD risk is whether the autistic traits in FXS are really the same as those existing in individuals with idiopathic ASD. Alternatively, do these behaviors instead represent the severe end of a continuum of cognitive and behavioral difficulties present in more affected individuals (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010)? Even if the symptoms appear the same, could ASD symptoms in FXS be manifestations of different underlying cognitive or emotional mechanisms to those that drive similar behaviors in idiopathic ASD?

One prominent account suggests that autistic symptoms in FXS are a “category mistake,” meaning that ASD and FXS are placed in the same category despite stemming from different levels of explanation (behaviorally versus biologically defined). These researchers argue that ASD behaviors in FXS are in fact explained by the low IQ associated with individuals with FXS (Hall et al., 2010). These researchers found dissimilar autistic symptoms in those diagnosed with FXS and ASD and those with idiopathic ASD, and showed a negative association between autistic behaviors and IQ. However, other studies reported little to no differences in autistic symptoms (e.g., Rogers et al., 2001). In addition, other genetically identified syndromes, like for example Williams syndrome, give evidence for a distinction between overall cognitive ability and social impairment, as individuals with this syndrome also present with low IQ yet are hyper-social. Indeed, a recent meta-analysis shows that low IQ is

characteristic of many genetically-defined disorders, but ASD symptoms are not (C. Richards, Jones, Groves, Moss, & Oliver, 2015).

A parallel emerges when considering the mechanisms responsible for the presence of hyperactivity and inattention in ADHD and FXS + ADHD (Scerif & Baker, 2015). Surprisingly, very few studies pit “idiopathic ADHD” against co-occurring FXS and ADHD as is done with ASD. Additionally, the hypothesis that ADHD symptoms are in fact a result of the low IQ associated with FXS (similar to the argument described above with ASD), has not been tested thus far. However, as in the case with ASD, not all children with low IQ have the same ADHD profiles, and there is a distinct lack of meta-analyses or systematic reviews of ADHD symptoms in genetic disorders, including FXS (Scerif & Baker, 2015). In fact, there is evidence that low IQ does not predict the severity of ADHD symptoms in young children with FXS (Cornish et al., 2012). Moreover, ADHD symptoms do not remain unchanged, but show developmental progression in FXS, suggesting again the significance of understanding symptoms over time (Wheeler et al., 2014).

Importantly, again similar to the argument made with ASD in FXS, the earlier age of diagnosis of FXS compared to ADHD allows for prospective longitudinal analysis of early markers of ADHD. Currently, prospective studies of ADHD are limited; investigating infants and young children at familial risk for ADHD in a similar manner to the autism literature is difficult due to the larger age gap necessary between siblings (familial risk is defined as having an older sibling with the diagnosis, and children with ADHD are on average diagnosed around age 7). Although some work has investigated familial risk by way of parent symptoms (Auerbach et al., 2008), a prospective investigation of ADHD symptoms could also be achieved by investigating young children with FXS.

In addition to lack of research investigating ADHD symptoms in genetic syndromes in general and FXS in particular, an open research question asks about the comorbidity of behaviorally defined disorders in FXS – it is only with the most recent revision of the Diagnostic and Statistical Manual of the American Psychiatric Association that comorbid diagnoses of idiopathic ASD and ADHD can be allocated, and have therefore become the focus of intensive study. Prospective longitudinal studies of risk to date (e.g., BASIS, <http://www.basisnetwork.org/>) are unbalanced, because participants are identified because of high risk for either ASD or ADHD, and not both. Although not tested statistically, Sullivan and colleagues (2006) note that boys with the full FXS mutation and clinical ASD levels met the ADHD diagnosis at higher rates than those who did not meet the ASD cut-off, suggesting a high comorbidity in FXS. In addition, parent surveys reveal FXS to have higher rates of diagnosed ASD and ADHD when comparing the four most common neurogenetic syndromes, although the authors of the study do not investigate the overlap of ASD and ADHD (C. Reilly, Senior, & Murtagh, 2015). Similarly, another national parent survey of co-occurring conditions in FXS report that ASD rarely occurs in isolation in FXS and is more likely accompanied by problems with attention, anxiety and hyperactivity (D. B. Bailey, Raspa, Olmsted, & Holiday, 2008).

In addition to these very few studies describing comorbidity of ASD and ADHD in FXS, although studies have investigated longitudinal predictors (cognitive or affective) of ADHD and ASD symptoms in FXS separately, no study to our knowledge has looked at the longitudinal relationship *between* ADHD and ASD symptoms in FXS. The current study sought to address this open question, by analyzing ADHD and ASD symptoms in children with FXS at three timepoints. If there is a relationship between ASD and ADHD symptoms in FXS, as the high comorbidity suggests, will ADHD

symptoms predict ASD symptoms over developmental time? Or will ASD symptoms predict ADHD symptoms? Or do they both predict each other? If both predict each other, this is suggestive of some underlying mechanism contributing to both ASD and ADHD symptoms, such that treating either symptom group will result in the reduction of both. If the relationship is unidirectional, this may suggest that symptoms of one disorder exacerbate and/or contribute to symptoms of the other. A unidirectional relationship of this kind may have implications for understanding the impact of atypical attention on ASD—the first aim of the current thesis.

Methods and materials

Participants

Fifty-nine boys with a confirmed diagnosis of fragile X syndrome were recruited through the Fragile X Society, the national support group for children and families with FXS in the United Kingdom (see Table 8 for demographics). These children were recruited as a part of a larger study of attention difficulties in boys with FXS, from which several papers have been published (Cornish et al., 2012; 2013; Scerif et al., 2012). Children were followed and assessed at three timepoints: time 1 (T1), 12 months after T1 at time 2 (T2), and 24 months later than T1 at time 3 (T3). Signed informed consent was obtained from all parents following the ethical procedures approved by the appropriate local institutional review board.

Table 8
Demographic data

	T1			T2			T3		
	<i>n</i>	<i>M(STD)</i>	Range	<i>n</i>	<i>M(STD)</i>	Range	<i>n</i>	<i>M(STD)</i>	Range
CA (mo.)	59	98.31(27.15)	38-133	59	110.68 (27.24)	49-146	59	122.63(27.37)	60-158
MA (mo.)	50	56.94 (10.09)	32-77	55	56.55 (12.35)	24-79	58	58.03(9.57)	24-80

CA = chronological age, MA = mental age, as determined by the Leiter-R. T1 = time 1, T2 = time 2, T3 = time 3, STD = standard deviation.

Several children were taking medication for the treatment of inattention and hyperactivity symptoms during the course of the study. However, the study sample contained a relatively small proportion of children on stimulant medication (7 out of 59 at T1, 6 out of 59 at T2, and 9 at T3 [i.e., a maximum of 15.3%, with 2 children among these having started but then discontinuing stimulant treatment]) (see Cornish et al., 2012 for discussion on why this may be the case), compared with stimulant medication rates reported for other samples of boys with fragile X syndrome (e.g., 33.4% in Sullivan et al., 2006). Due to the potential for medication to confound measures of ADHD symptomatology, we ran analyses both including and excluding these children.

The parents of several of the children also reported a clinical diagnosis of ASD or ADHD. Although these were not confirmed further than through parent report, and parents were not asked for every child at every timepoint, we note them here for descriptive purposes: seven children were diagnosed with ASD and two children were diagnosed with ADHD at T1; 4 children were diagnosed with ASD and 2 children were diagnosed with ADHD at T2; and 1 child diagnosed with ASD, 2 diagnosed with ADHD at T3.

Measures

Intellectual ability

The Leiter International Performance Scale-Revised (Leiter-R) (Roid & Miller, 1997) was used to measure intellectual ability, as it is a standardized assessment for individuals aged 2-20 years that is entirely nonverbal. This measure was chosen because some children with FXS struggle with verbal instruction as well as providing verbal responses. The brief IQ score is composed of four different subscales: figure ground segregation, form completion, sequential ordering, and detecting repeated patterns. The

figure ground segregation task involved detecting items embedded in increasingly detailed backgrounds. The form completion task required fitting together pieces into a complex whole. The sequential ordering required ordering image sets by logical rules, including color, number, size, etc. Detecting repeated patterns involved identifying and continuing series of increasingly complex patterns.

The Leiter-R allows for computing not only a brief IQ score, which is based off of a normative sample, but also growth scores. Growth scores are scaled such that all items in the battery are made comparable by transforming raw-score scales to an equal-interval Rasch Scale (Rasch, 1960). In this way, item difficulty is not based on the proportion of participants answering the item correctly within a given sample, which is ability-level dependent, but is rather sample independent. Growth scores range from 380 to 560 and provide a measure based on the domain of all skills tapped by the Leiter-R, as opposed to the norm sample. This method is helpful when comparing performance over multiple occasions as well as when working with children with significant delays or low abilities, as in the current study.

Autistic symptomatology

The Social Communication Questionnaire (SCQ; Rutter et al., 2003) was used to measure autistic symptoms at each timepoint. The SCQ is a brief (10 minute) questionnaire, filled out by a parent or other primary caregiver, which measures communication skills and social functioning in children who may meet diagnostic criteria for ASD. The SCQ is used with children older than 4 years, which was the case for all participants in the current study except for two at T1. This instrument is typically used to determine whether children should be referred to further services for a full ASD evaluation. It provides both a total raw score (including an at-risk cut-off) as well as

three subscales: Reciprocal Social Interaction, Communication, and Restricted or Repetitive Interests. Parents of the participants in the current study filled out the SCQ at each timepoint, and only the total raw score was used.

ADHD symptomatology

The Conners Teacher Rating Scale (CTRS; C. K. Conners, 1997b) and the Conners Parent Rating Scale (CPRS; C. K. Conners, 1997a) were used to measure behavioral inattention-hyperactivity. These commonly used measures screen for attention-deficit/hyperactivity disorder (ADHD) in both the home (CPRS) and the classroom (CTRS) for children 3-17 years old. These instruments consist of 28 items in the short form, with three subscales addressing Oppositional Behavior Problems, Hyperactive Behavior, and Cognitive-Inattention Problems. In addition to these subscales, the CTRS and CPRS provide both a raw and t-score normed ADHD Index, which provides a composite score from key items across the subscales. Children with scores above the clinical cut-off (70) are considered likely to have ADHD while those above 65 are considered at-risk.

Problem behaviors

In addition to autistic and ADHD symptomatology, the teacher-rated Strengths and Difficulties Questionnaire (SDQ; R. Goodman, Ford, Simmons, Gatward, & Meltzer, 2000b) was used to measure emotional and behavioral symptoms, to provide potential cross-validation against the scores obtained through SCQ and Conners CTRS and CPRS. The SDQ consists of 25 items and is scored according to five subscales: hyperactivity (related to ADHD), emotional problems, conduct problems, peer relationship problems, as well as prosocial behavior (related to ASD). The current study

focused on hyperactivity and prosocial behavior, in order to determine if these measures relate to our measures of ASD and ADHD symptomatology.

Data analysis

Mixed effects modeling

Mixed effects models were specified using the *lme4* package in *R* (Bates et al., 2015). For each dependent measure, a model was specified with a fixed effect of time (T1, T2, T3), a random slope of time and random effect of participant. Similar to Chapter 2, *p*-values were determined using the Kenward-Roger approximation for degrees of freedom (Kenward & Roger, 1997) as implemented by the *afex* package in *R* (Singmann et al., 2015).

Structural equation modeling (SEM)

SEMs were specified using the *lavaan* package in *R* (Rosseel, 2012). The maximum likelihood estimation with robust (Huber-White) standard and a scaled test statistic that is (asymptotically) equal to the Yuan-Bentler test statistic was used, in order to account for potentially non-normally distributed data. In addition, *lavaan*'s case-wise full information maximum likelihood estimation was used to account for missing data. However, this procedure requires data to be missing at random (MAR) or missing completely at random (MCAR), which was unlikely to be the case in the current study. For this reason, SEMs were run with and without this missing data procedure.

Results

Measure comparison

Non-parametric Spearman's Rho correlation tables were created in order to investigate relationships between parent- and teacher-rated measures of ASD and ADHD, as well as their relationship to IQ. These correlations were not corrected for multiple comparisons. Descriptive statistics can be seen in Table 9.

ADHD measures

Whereas the two teacher-rated measures of ADHD symptoms (SDQ Hyperactivity and CTRS ADHD index score) were highly correlated, the parent-rated measure (CPRS ADHD index score) only highly correlated with the CTRS ADHD index score at T1, and did not correlate strongly with the SDQ. In addition, IQ only correlated with the CTRS ADHD index score, but not the SDQ or CPRS ADHD index score (Table 10).

ASD measures

The teacher-rated (SDQ prosocial) and parent-rated (SCQ) measures of ASD symptoms did not highly correlate, except T3 SCQ and T2 SDQ. In addition, IQ strongly correlated with SCQ at T1, but not strongly with the SDQ (Table 11).

Measure trajectories

Mixed effects modeling revealed a significant effect of time for predicting CPRS ADHD index scores, $F(1, 96.27) = 7.34$, $p = 0.008$, with CPRS ADHD index scores decreasing over time (unstandardized estimate = -1.21, see Table 9). The same was true for predicting IQ scores, $F(1, 104.68) = 50.44$, $p < 0.001$, with brief IQ scores decreasing over time (unstandardized estimate = -4.76, see Table 9). There was no significant effect of time for the SCQ, $p = 0.17$.

Table 9
Descriptive statistics for study measures

	<u>CPRS</u>			<u>SCQ</u>			<u>CTRS</u>			<u>IQ</u>			<u>SDQ Hyperactivity</u>			<u>SDQ Prosocial behaviors</u>		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
N	51	50	49	51	50	49	54	54	52	50	55	58	54	54	54	54	54	54
Min	49	53	47	5	0	4	48	47	45	40	36	36	2	3	3	0	0	0
Max	85	82	82	33	34	36	80	88	84	109	95	93	10	10	10	10	10	10
Mean	71.04	70.52	69.1	19.88	20.16	21	66.44	64.78	67.38	62.14	55.56	51.55	7.96	7.93	7.69	4.91	5.07	5.13
STD	8.91	8.05	9.96	7.32	7.60	8.67	7.93	8.94	10.00	14.94	15.00	12.78	1.93	2.14	2.32	2.92	3.28	3.34

Note: CPRS = Conners Parent Rating Scale ADHD index score, SCQ = Social Communication Questionnaire, CTRS = Conners Teacher Rating Scale ADHD index score, IQ = Leiter-R brief Intelligence Quotient, SDQ = Strengths and Difficulties Questionnaire, STD = standard deviation.

Table 10

Spearman's Rho correlation table for parent- and teacher-rated ADHD symptoms and IQ

	1	2	3	4	5	6	7	8	9	10	11	12
1. T1 IQ	1	.734**	.706**	-0.063	-0.134	-0.195	-0.148	-.431**	-0.287	0.049	-0.25	-0.145
	50	48	49	46	44	42	46	46	44	46	46	46
2. T2 IQ	1		.773**	-0.146	-0.137	-0.163	-0.168	-.292*	-0.274	-0.13	-0.072	-0.036
	55		54	49	49	48	50	50	48	50	50	50
3. T3 IQ	1			-0.009	0.049	0.033	-0.02	-.273*	-.359**	0.037	-0.083	0.02
	58		58	51	50	49	53	53	51	53	53	53
4. T1 CPRS	1				.871**	.713**	.396**	0.118	0.139	0.29	0.146	0.106
	51			51	48	46	46	46	44	46	46	46
5. T2 CPRS	1					.781**	.371*	0.151	0.108	.319*	0.156	0.162
	50				50	46	45	45	43	45	45	45
6. T3 CPRS	1						.463**	.320*	0.266	.378*	.348*	0.288
	49				49	49	44	44	42	44	44	44
7. T1 CTRS	1							.554**	.432**	.622**	.364**	.465**
	54						54	53	50	54	53	52
8. T2 CTRS	1								.507**	.314*	.768**	.480**
	54							54	50	53	54	52
9. T3 CTRS	1									.319*	.322*	.699**
	52								52	50	50	52
10. T1 SDQ Hyperactivity	1										.302*	.472**
	54										53	52
11. T2 SDQ Hyperactivity	1											.416**
	54											52
12. T3 SDQ Hyperactivity	1											
	54											

Note: CPRS = Conners Parent Rating Scale ADHD index score, CTRS = Conners Teacher Rating Scale ADHD index score, SDQ = Strengths and Difficulties Questionnaire, IQ = Leiter-R brief Intelligence Quotient. First line is Spearman's Rho, second line is sample size. Sample sizes vary due to missing data.

Table 11

Spearman's Rho correlation table for parent- and teacher-rated ASD symptoms and IQ

	1	2	3	4	5	6	7	8	9
1. T1 IQ	1	.734**	.706**	-.447**	-.331*	-.301	0.112	0.126	0.057
	50	48	49	46	44	42	46	46	46
2. T2 IQ	1		.773**	-.381**	-.0272	-.024	0.243	0.272	.304*
	55	54	54	49	49	48	50	50	50
3. T3 IQ	1			-.415**	-.342*	-.0243	0.148	0.149	0.185
			58	51	50	49	53	53	53
4. T1 SCQ	1				.809**	.711**	-.0255	-.0283	-.0.118
				51	48	46	46	46	46
5. T2 SCQ	1					.792**	-.0204	-.022	-.0.198
					50	46	45	45	45
6. T3 SCQ	1						-.029	-.437**	-.0.288
						49	44	44	44
7. T1 SDQ Prosocial behavior	1						1	.725**	.675**
							54	53	52
8. T2 SDQ Prosocial behavior	1							1	.671**
								54	52
9. T3 SDQ Prosocial behavior	1								1
									54

Note: IQ = Leiter-R brief Intelligence Quotient, SCQ = Social Communication Questionnaire, SDQ = Strengths and Difficulties Questionnaire. First line is Spearman's Rho, second line is sample size. Sample sizes vary due to missing data.

Structural equation modeling (SEM)

CPRS ADHD index

First, SEM was used with the parent rating scale for ADHD (CPRS ADHD index score) and ASD (SCQ) symptomatology to create an autoregressive cross-lagged model with three timepoints. As severity of cognitive impairment, as measured by IQ, may have a confounding effect on ADHD and ASD symptomatology, one model was run including IQ as a predictor over time. In addition, due to the range in ages in which children entered the study (3-11-years-old at T1), a separate model was run with chronological age (CA) at T1 as a predictor for ADHD and ASD symptomatology over time.

The model using robust maximum likelihood and including the Leiter-R brief IQ at T1 and T2 (Figure 7; model fit: $\chi^2(9) = 7.04$, $p = 0.633$, comparative fit index [CFI] = 1.00, Tucker-Lewis index [TLI] = 1.03) revealed significant predictive relationships from T1 to T2 and from T2 to T3 for both the CPRS and SCQ separately. In addition there was one cross-measure relationship, with the CPRS at T2 predicting SCQ at T3. There were no relationships with the brief IQ². These relationships held when only including participants with no missing data ($n = 41$), and also when excluding those participants who were taking medication for inattention and/or hyperactivity ($n = 48$), as well as excluding participants with missing data and those taking medication ($n = 34$, although a particularly small sample). These relationships also hold when using the CPRS ADHD index raw scores as opposed to t-scores, in order to match the SCQ scores, which only have raw scores. These relationships also hold when using Leiter-R growth scores as opposed to brief IQ.

² These results are the same when including the CPRS cognitive/inattentive subscale and SCQ reciprocal social interactions subscales instead of total scores.

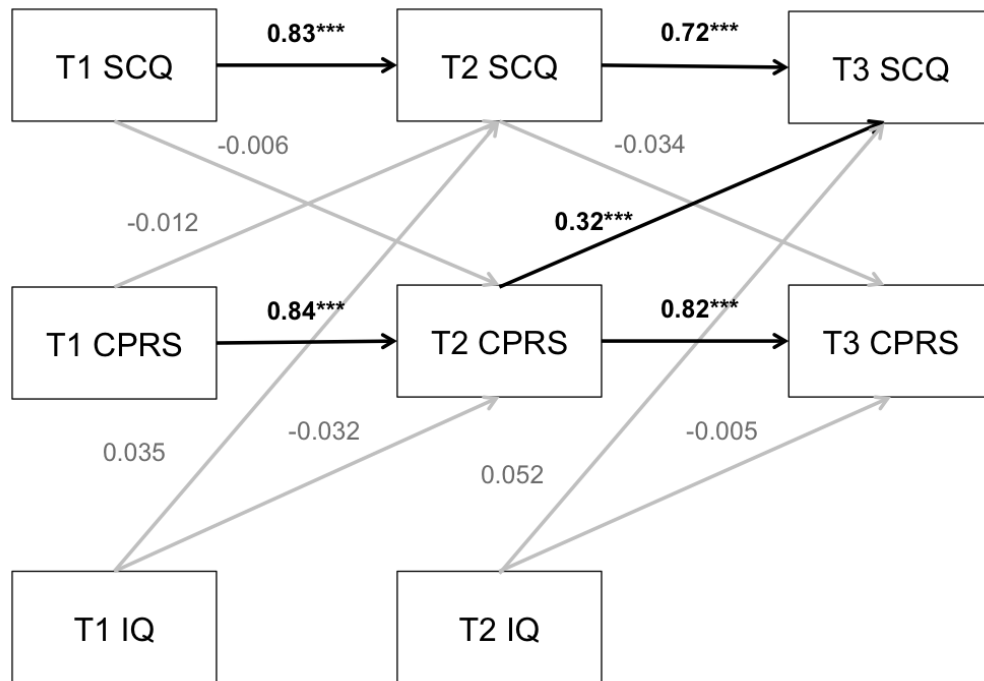


Figure 7. Autoregressive cross-lagged path analysis for ASD symptoms (Social Communication Questionnaire: SCQ), and ADHD symptoms (Conners Parent Rating Scale ADHD index: CPRS) over three timepoints in boys with FXS, including Leiter-R brief IQ. T1 = entry, T2 = 12 months later, T3 = 24 months later. Standardized regression estimates marked with *** are $p < 0.001$. Dark lines are significant regression estimates.

The model using robust maximum likelihood and including CA at T1 (Figure 8; model fit: $\chi^2(5) = 5.86$, $p = 0.320$, comparative fit index [CFI] = 1.00, Tucker-Lewis index [TLI] = 0.98) revealed significant predictive relationships from T1 to T2 and from T2 to T3 for both the CPRS and SCQ separately. In addition there was one cross-measure relationship, with the CPRS at T2 predicting SCQ at T3. There was only a

marginally significant relationship between T1 CA and T3 SCQ ($p = 0.081$)³. These relationships held when only including participants with no missing data ($n = 45$), and also when excluding those participants who were taking medication for inattention and/or hyperactivity ($n = 48$), as well as excluding participants with missing data and those taking medication ($n = 36$, although a particularly small sample). These relationships also hold when using the CPRS ADHD index raw scores as opposed to t-scores, with the addition of a significant relationship between T1 CA and T3 SCQ.

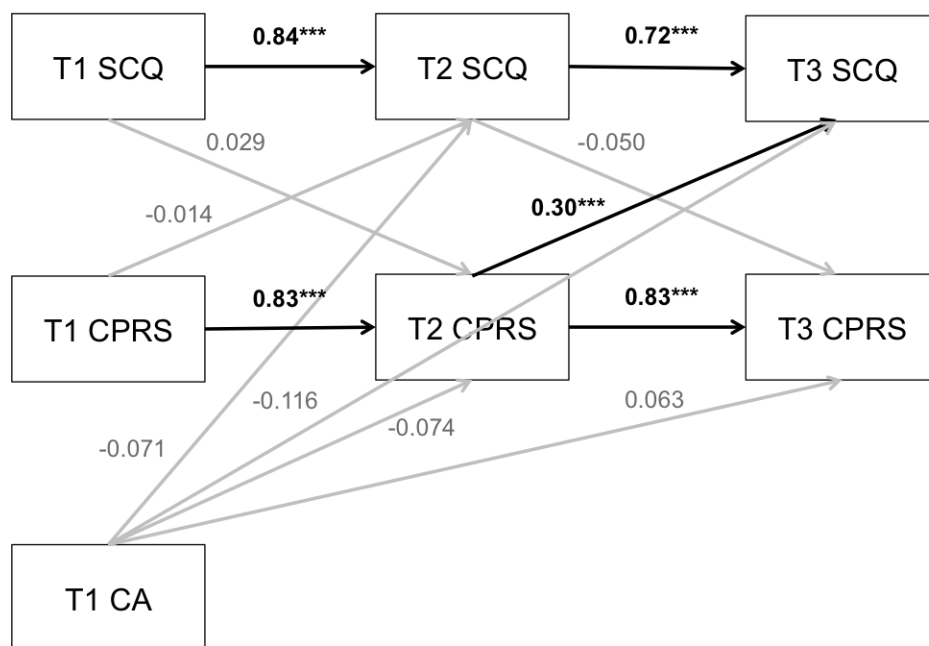


Figure 8. Autoregressive cross-lagged path analysis for ASD symptoms (Social Communication Questionnaire: SCQ), and ADHD symptoms (Conners Parent Rating Scale ADHD index: CPRS) over three timepoints in boys with FXS, including chronological age (CA) at entry. T1 = entry, T2 = 12 months later, T3 = 24 months later. Standardized regression estimates marked with *** are $p < 0.001$. Dark lines are significant regression estimates.

³ These results are the same when including the CPRS cognitive/inattentive subscale and SCQ reciprocal social interactions subscales instead of total scores, with the addition of a significant relationship between T1 CA and T3 SCQ ($p = 0.010$)

CTRS ADHD index

To see if ADHD measures vary when using teacher report instead of parent report for ADHD symptomatology, the same SEM models were run including CTRS ADHD index score. However, sample size of children with no missing data was smaller for teacher report ($n = 32$) compared to parent report ($n = 41$).

The model using robust maximum likelihood and including the Leiter-R brief **IQ** at T1 and T2 (model fit: $\chi^2(9) = 13.06$, $p = 0.160$, comparative fit index [CFI] = 0.97, Tucker-Lewis index [TLI] = 0.93) revealed significant predictive relationships from T1 to T2 and from T2 to T3 for both the CTRS and SCQ separately. In addition, IQ at T1 significantly predicted CTRS at T2. However, the relationship between CTRS at T2 predicting SCQ at T3, as seen with the CPRS above, was not present. These relationships hold when excluding children taking medication for inattention and/or hyperactivity ($n = 48$), but the relationship between IQ at T1 and CTRS at T2 is absent when excluding children with missing data ($n = 32$). There were far too few participants when excluding participants with missing data and those taking medication ($n = 26$) therefore this analysis was not included.

The model using robust maximum likelihood and including **CA** at T1 (model fit: $\chi^2(5) = 12.95$, $p = 0.024$, comparative fit index [CFI] = 0.94, Tucker-Lewis index [TLI] = 0.79) revealed significant predictive relationships from T1 to T2 and from T2 to T3 for both the CTRS and SCQ separately. In addition there was a significant relationship between CA at T1 and SCQ at T3 and a marginally significant relationship between SCQ at T1 and CTRS at T2 ($p = 0.070$). When only including participants with no missing data, the relationship between CA at T1 and SCQ at T3 no longer holds ($n = 35$). When excluding participants taking medication, both the relationship between CA

at T1 and SCQ at T3 and the marginal relationship between SCQ at T1 and CTRS at T2 no longer hold ($n = 48$). There were far too few participants when excluding participants with missing data and those taking medication ($n = 27$) therefore this analysis was not included.

Discussion

The current study investigated the longitudinal relationships between ADHD and ASD symptoms in a population at high risk for both: boys with fragile X syndrome. As expected, we found strong relationships over three timepoints, each a year apart, for ADHD symptoms (as measured by the parent-rated Conners scale) and ASD symptoms (as measured by the SCQ). In addition, we found that ADHD symptoms at T2 predicted ASD symptoms at T3, suggestive of a causal relationship (although further work is necessary to address this claim more directly, see below). Importantly, these relationships hold when including CA at entry to the study, as well as when including severity of impairment as measured by IQ, and their effects on both ASD and ADHD symptoms do not reach significance. However, this cross-measure relationship does not occur when using the teacher-rated Conners scale.

There are several possible explanations for this discrepancy. It is clear from the lack of correlation that the parent-rated questionnaires (SCQ, CPRS) and the teacher-rated questionnaires (SDQ, CTRS) are tapping into different behaviors. In particular, while the parent measures do not relate to IQ, there are relationships between IQ and the CTRS. Perhaps the parent-rated version is a more accurate measure of ADHD in the sense that it is not confounded with IQ. Indeed, the current study is not the only study to have found differences between parent and teacher ratings of ADHD symptoms (Bralten et al., 2013; De Los Reyes & Kazdin, 2005; Willcutt, Hartung, Lahey, Loney, & Pelham, 1999), leading to various explanations, including the following: 1) although

parent and teachers may be observing the same phenotype, they bring their own separate rater biases, and 2) children may be behaving differently at home than in school and therefore teacher and parent raters are in fact observing different phenotypes (N. Martin, Scourfield, & McGuffin, 2002). Importantly, there is evidence that while parents are more biased in rating ADHD symptoms than teachers, when utilizing ratings from multiple teachers for one child the teacher ratings present more bias (Christie A Hartman, Rhee, Willcutt, & Pennington, 2007). As the current study uses teacher ratings from several teachers over a 3-year period, the parent ratings are perhaps the more appropriate measure to use.

Another complication is the fact that the current study only utilized the parent-rated SCQ. Perhaps cross-measure relationships would be present with the CTRS when also using a teacher-rated SCQ. Finally, although overall teachers were more successful than parents in filling out questionnaires at all three timepoints, the pattern of missing data was such that there were fewer children with complete datasets when using teacher-report measures. For example, when including IQ in the model, only 32 children had complete datasets with teacher-report measures. Given the rule of thumb that analyses should have 5 samples per parameter at a minimum, and our models contained 12 parameters, more caution is warranted when interpreting the models including teacher-report measures.

With these caveats in mind, the current study has contributed to several of the debates and open questions discussed above. The current study has expanded the small literature investigating comorbidity of behaviorally-defined disorders within FXS (D. B. Bailey et al., 2008; C. Reilly et al., 2015; K. Sullivan et al., 2006) by looking at both ASD and ADHD symptoms over developmental time, in order to go beyond cross-sectional analysis and investigate potential causal relationships. It also adds to the

literature suggesting that low IQ does not underpin ASD symptoms in FXS over time (Hernandez et al., 2009), by showing that IQ does not relate to SCQ scores.

Interesting to note is that the relationship between ASD and ADHD symptoms only occurred between the later timepoints (T2 to T3), and not from T1 to T2. It is well known that ASD symptoms mostly remain persistent over time (e.g., Charman et al., 2005), while ADHD symptoms are more variable across development (e.g., J.-O. Larsson, Larsson, & Lichtenstein, 2004). This pattern can also be seen in the current study with no change over time for SCQ scores, but decreasing CPRS scores. It is possible that ADHD symptoms in FXS only contribute to ASD symptoms later in development, once ADHD symptoms have stabilized. ASD and ADHD traits are also more difficult to measure in early childhood, which could contribute to this pattern. Finally, previous literature suggests that ASD and ADHD symptom co-occurrence is highest in adolescence (Catharina A Hartman, Geurts, Franke, Buitelaar, & Rommelse, 2016). These explanations are consistent with the literature that suggests increasing genetic correlation between ASD and ADHD traits with increasing age (Rommelse & Hartman, 2016).

Moreover, the current study has possible important implications for the literature on comorbidity between ASD and ADHD in general, beyond FXS. The debate about the relationships between ASD and ADHD is ongoing. While some studies comparing “pure” ASD and ADHD to comorbid ASD+ADHD suggest distinct profiles of impairments that are additive in comorbid cases and therefore give weight to the hypothesis that ASD and ADHD represent separate disorders (e.g., Tye et al., 2014), others postulate that ASD and ADHD are manifestations of the same overarching disorder (e.g., Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Other important work looking beyond diagnostic criteria to investigate latent classes from ASD and

ADHD symptoms gives evidence to this overarching disorder hypothesis, suggesting that “pure” ADHD is a milder subtype within the ASD spectrum (which excludes the presence of “pure” ASD) (van der Meer et al., 2012). However, to our knowledge only two studies have investigated the relationships between ASD and ADHD symptoms over time (St Pourcain et al., 2011; Taylor et al., 2013). We believe it is of great theoretical importance to do so, because regardless of whether these disorders are distinct or overlapping, it is an open question whether one (or both) contributes to the other (or each other). The current study converges with the previous two longitudinal studies, which suggest a stronger predictive relationship of ADHD symptoms on ASD symptoms over development as opposed to the reverse (St Pourcain et al., 2011; Taylor et al., 2013). Importantly, while the previous studies found this relationship in the general population, we found it in children with FXS, who are at high risk for both ASD and ADHD, making these findings potentially more clinically relevant.

The unidirectional relationship between ASD and ADHD symptoms in FXS also has important implications for treatment. If replicated in other samples, this finding suggests that targeting ADHD symptoms may improve ASD symptoms. Further, this hypothesis could be tested in a more causal manner by intervention. Although several previous studies (not investigating children with FXS) have reported that stimulant medication in individuals with comorbid ASD and ADHD (or individuals with ASD and ADHD symptoms) has alleviated ADHD symptoms, but had little or no effect on ASD symptoms (if tested at all) (Handen, Johnson, & Lubetsky, 2000; Hazell, 2007), some have reported small improvements (Jahromi et al., 2009; Pearson et al., 2013). However, these studies did not have follow-ups longer than several weeks to months. Social cognition is, in part, learned, and not instantaneous. Moreover, as the current study suggests, ADHD symptoms have their effects on ASD symptoms over developmental

time. Future work should therefore investigate long-term longitudinal intervention to give further support to the conclusions drawn from the current study.

One limitation is the instrument used to measure ASD symptoms. While the Conners scale is considered to be the gold standard for assessing ADHD symptoms, a more appropriate method for assessing ASD symptoms would perhaps be the Autism Diagnostic Interview (ADI) and/or the Autism Diagnostic Observation Schedule (ADOS). Future study should include these measures as well.

By investigating ASD and ADHD symptoms longitudinally within children with FXS, the current study contributes to both the FXS literature, as well as to the ongoing debate on the comorbidity of ASD and ADHD symptoms. We show that the relationship between ASD and ADHD symptoms over time is unidirectional, with ADHD symptoms predicting ASD symptoms later in childhood. This finding informs both the comorbidity of the two disorders in FXS, which has been little researched, as well as providing future directions of study of how ADHD symptoms and their treatment may affect individuals with ASD.

Importantly, this work has implications for the current thesis. Chapters 2 and 3 were designed to determine the impact of atypical non-social attention on social impairment, to preliminarily address the potentially causal role of atypical attention in ASD. While Chapter 2 examined relationships between atypical non-social attention and social impairment at the cognitive level in young children at familial risk for ASD, the current chapter complimented this work by investigating the symptoms level in children with FXS. Crucially, we wish to acknowledge that considering ADHD symptoms to be “atypical non-social attention” at the symptoms level, and “atypical non-social *selective* attention” in particular (akin to the selective attention implicated in Chapter 2), is not uncontroversial. Although early studies examining cognitive impairments in ADHD

focused on selective attention (Brodeur & Pond, 2001; Jonkman, Kenemans, Kemner, Verbaten, & Van Engeland, 2004), the more recent literature has turned to more traditional executive function skills, most notably inhibition (Alderson, Rapport, & Kofler, 2007; Booth et al., 2005). It is also naïve to consider ADHD to be a unitary phenomenon, just as it is naïve to consider ASD to be one. However, investigating the symptoms level has clearer clinical implications, and therefore we believed the analysis to be of importance, despite this caveat. Additionally, investigating the cognitive/inattentive and reciprocal social interaction subscores of the CPRS and SCQ instead of the total scores, which are potentially closer to the cognitive measures studied in the previous chapter, offered the same results.

With Chapters 2 and 3 investigating the first question of this thesis, we turn to the second question with the next chapter—if a lack of a privileged status for social stimuli is a part of the atypical attention cascade in ASD, how does this atypical attention bias lead to the social interaction impairments that define the disorder?

Chapter 4: The functional consequences of social attention/inattention: Memory for complex scenes and relation to autistic traits and social anxiety

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Candidate contribution: The candidate significantly contributed to every stage of this study, including: experimental design and implementation, recruitment, data collection, analysis strategy, data analysis, and written report.

Introduction

While non-social selective attention may play an early role in an atypical attention framework of ASD, and may contribute to an altered, more domain-specific social attention bias (as described in Chapter 1), an altered social attention bias may further contribute in a cascading manner to the development of impaired social functioning in ASD. One potential mechanism by which this may occur is that reduced attention to social stimuli may result in an individual learning and remembering less about people and the social world, which could lead to difficulty in social interactions. The current chapter, as well as the two following it, will investigate this hypothesis by assessing the functional consequences of a social attention/inattention bias on learning and memory, as well as subsequent attentional orienting guided by experimentally induced memories.

Decades of research have suggested that faces and social stimuli hold a privileged processing status in human cognition. Studies have reported increased perceptual sensitivity to faces in newborn babies, which led to the proposal that infants are born with an innate structural representation of faces (although the face-specificity of the perceptual mechanisms underlying face preference in infancy is debated: Cassia et al., 2004; Morton & Johnson, 1991). Neuroimaging has extended these findings to suggest brain areas (e.g., Puce et al., 1996) as well as single cells (e.g., Perrett et al., 1992) specialized for processing faces (although see Gauthier & Tarr, 1997 for evidence of perceptual sensitivity to non-faces after extensive training). In addition to perceptual sensitivity, faces are also suggested to play a special role in selective attention (Vuilleumier, 2000; Vuilleumier et al., 2001), including in change-detection tasks (Ro et al., 2001) and cueing tasks (Langton & Bruce, 1999).

A less commonly used alternative to investigate how social stimuli affect selective attention is the case of social *distraction* when people are *not* the targets of attention. Distractor faces show interference effects in visual search even under high perceptual load, suggesting mandatory processing (Lavie et al., 2003). Additionally, neurotypical adults and children have been reported to take longer to detect a target in a simple search paradigm with a face as a distractor than when there is no face distractor (Langton, Law, Burton, & Schweinberger, 2008; Riby et al., 2012). Interestingly, this effect does not extend to autistic children (Riby et al., 2012), whose reduced attention to faces and people is thought to demonstrate the absence of a privileged status for social stimuli (Klin et al., 2003), as discussed in Chapter 1.

However, surprisingly, and critically, the effects of such distraction have not been investigated beyond selective attention within perceptual tasks. Social distraction is likely to have downstream consequences, influencing how well individuals remember

information encountered during visual search. Studies reporting poorer memory due to general distraction at encoding are numerous, spanning both working memory (e.g., Awh & Vogel, 2008) and long-term memory (e.g., Foerde, Knowlton, & Poldrack, 2006). However, no studies have investigated the effect of *social distraction* on longer-term memory (see de Fockert, Rees, Frith, & Lavie, 2001; Mano et al., 2013 for working memory examples with distraction during maintenance), nor have they used search in naturalistic scenes instead of simple visual search. The current study addresses this important gap in the literature by investigating the consequences of social distraction during visual search in naturalistic scenes on the quality of subsequent memories.

We developed a task using natural scenes, which enabled us to contrast distraction caused by social stimuli vs. other, well-controlled stimuli that were matched for low-level visual properties. People are salient not just in terms of their social valence, but also with regards to low-level visual properties, including color and contrast. Although researchers often utilize scrambled or inverted faces, these control stimuli are less naturalistic and may pop out in natural scenes. The current study takes a novel approach to these problems, by using a graph-based visual saliency algorithm (Harel, Koch, & Perona, 2006) to ensure that the physical salience of social vs. non-social distractor items embedded within scenes is matched.

Finally, if social distraction does indeed have functional consequences, an individual's degree of bias towards social stimuli may play a moderating role. A large literature suggests a relationship between general anxiety and attentional bias towards threatening stimuli (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; S. Bishop, Duncan, Brett, & Lawrence, 2004), and this relationship has been reported specifically for social anxiety and emotional faces in both clinical and

typical populations. (e.g., Amir, Elias, Klumpp, & Przeworski, 2003). In contrast to highly socially anxious individuals, as mentioned in Chapter 1, there is ample evidence that autistic individuals are less engaged by social stimuli in general, and more specifically do not demonstrate social distraction in simple visual search. We took advantage of these well-characterized individual differences, by including scales that tap into hypersensitivity to social stimuli (social anxiety) versus insensitivity to social stimuli and social distraction (autistic traits) (however, please see Senju & Johnson, 2009 for competing theories of hypo- versus hyper- arousal to social stimuli in ASD).

In order to understand the consequences of social distraction for attention and subsequent memory, we posed three complementary questions: 1) Will the previously documented social-distraction effect extend to visual search in natural scenes and when compared to distraction from items that are matched for visual salience? 2) Will social distraction influence later memory performance, such that memory will be poorer for social scenes? 3) Will these relationships be moderated by individual differences in social anxiety or autistic traits?

Methods and materials

Participants

The University of Oxford Central University Research Ethics Committee (CUREC) approved this research. Thirty-seven healthy adult volunteers participated (aged 19-33, 21 female). All had normal or corrected-to-normal vision. Six other participants were tested but excluded—four due to age outside of our range of interest (18-35), one due to eye-tracker malfunction, and one due to lack of English proficiency to understand task instruction. Sample size was determined by the desire to at least double the size of previous studies, which had sample sizes of 16 (Patai, Doallo, &

Nobre, 2012; Stokes, Atherton, Patai, & Nobre, 2012a), in order to detect individual differences. Our stopping rule was to stop testing when our sample size was a multiple of four, due to the number of counterbalanced groups (see below). All participants provided written informed consent and were paid for their participation or received course credit.

Stimulus design and visual salience computation

Eighty natural indoor and outdoor scenes were prepared from photographs taken by the experimenter (BD) or acquired from the Internet with permission (1000 x 750 pixel resolution in 32-bit color, under the experimental conditions spanning 37.05 by 22.34 degrees of visual angle). Target objects were photographs of objects including tools, toys, fruits, etc., sized to approximately 1.09 by 1.09 degrees of visual angle. Social distractor stimuli were prepared from photographs of people standing upright taken by the experimenter (BD). Non-social distractors were objects chosen to be similar to social distractors in terms of color and contrast (e.g., deck umbrella, ornamental plant, coat stand, etc.). They were also chosen to fit naturally into the scene such that they did not appear odd. All distractors were 9.03 degrees of visual angle in height.

Matching ‘social’ and ‘non-social’ versions of each scene were created using GIMP 2.8.10 image manipulation software with: 1) a social distractor (person) edited into a natural location or 2) a non-social distractor edited into the same location. Every scene had a unique target object within it. Target objects were superimposed during the visual search task through the stimulus presentation program. Target objects were not necessarily semantically related to the scenes, and were not necessarily placed in realistic locations.

Presentation of social and non-social scenes was counterbalanced across participants, so that half saw the same 40 scenes as social and the other 40 scenes as non-social, while the other half of the participants saw the reverse. In addition, each scene had two target locations that were counterbalanced across participants: one on the same side and the other on the opposite side of the distractor. These locations were balanced such that any one participant saw equal numbers of targets in the four visual quadrants. Finally, distractor position and gender of social distractors were also balanced (Figure 9). Target location and distractor counterbalancing resulted in four participant groups: distractor group 1 location 1, distractor group 1 location 2, distractor group 2 location 1, distractor group 2 location 2.

Distractor type	40 social								40 non-social			
Distractor location	20 left				20 right				20 left		20 right	
Target location	10 same		10 opposite		10 same		10 opposite		10 same	10 opposite	10 same	10 opposite
Distractor gender	5F	5M	5F	5M	5F	5M	5F	5M	Not applicable			

Figure 9. Scenes balanced for distractor type, distractor location, target location, and distractor gender. Distractor location refers to screen hemifield. Target location is with respect to the distractor: same or opposite side of the distractor. Distractor gender (F: female, M: male) is only applicable to social scenes.

To ensure that social and non-social distractors were equally salient with regards to low-level visual properties (color, contrast, etc.), salience values were calculated using a bottom-up visual saliency algorithm based on the original Itti and Koch algorithm (Harel et al., 2006). For both target locations, paired samples t-tests

comparing social and non-social versions of all scenes revealed no significant differences in salience between: 1) social/non-social distractors identified with hand-drawn AOIs ($p > 0.250$), 2) social/non-social scenes overall ($p > 0.250$), and 3) social/non-social scene target objects in the target locations identified with circular AOIs ($p > 0.250$) (Figure 10). See Appendix II for more example stimuli.

Procedure

Visual search

Participants sat 75 cm away from a 1680 by 1050 resolution monitor (spanning 37.05 by 22.34 degrees of visual angle) with their chin on a chin rest. They were directed to look for target objects in 80 scenes over three blocks. During search, gaze position was recorded from both eyes at 500 Hz using an Eyelink 1000 infrared camera following a 9-point calibration and validation. For each trial, participants saw: 1) a fixation square for 1000-1500 ms, 2) the object alone (1.61 by 1.61 degrees of visual angle) for 3000 ms, 3) the scene and embedded object, and 4) feedback for 1000 ms (“Object not found” or “Object found” on blank screen). Maximum search time was 20 s in the first block and decreased by 4 s each subsequent block. Participants observed all 80 scenes in random order during each of three blocks. They were instructed to press the spacebar when they found the object to reveal the cursor and then click on the object (Figure 10). Accuracy in locating the target was defined as clicking on the object within 0.54 degrees of visual angle.

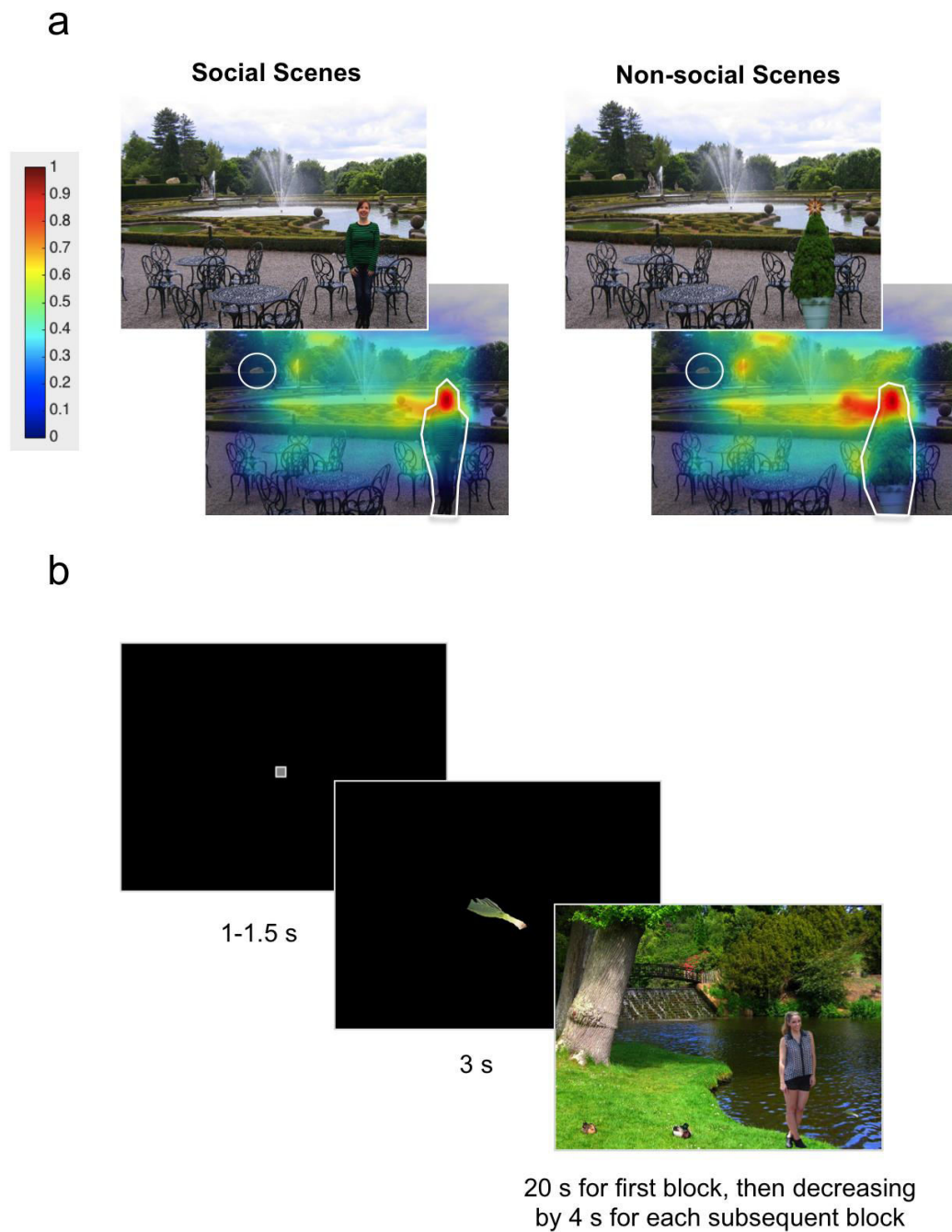


Figure 10. Scene salience and visual search procedure. A) Social and non-social scenes equated for salience. Salience values showed no significant differences in low-level visual properties (red indicates high salience values and blue indicates low values). Target and distractor AOIs (shown in white) were drawn using a circle, or freeform respectively. B) Visual search trial timeline. Each trial was followed by feedback (“Object not found” or “Object found” on a blank screen for 1 s).

Memory phase

After a short break (on average 4 minutes), explicit memory for target locations was probed. Participants saw each scene with its accompanying social/non-social distractor in a random order. The target appeared in the center of each scene and participants could move it around the scene with the mouse, indicating the remembered location with a mouse click.

Questionnaires

After the memory test, the participants filled out the autism-spectrum quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001)—a questionnaire designed to be sensitive to individual differences in the normal population—and the Liebowitz social anxiety scale (SAS) (Liebowitz, 1987).

Eye-tracking processing

Eye-tracking data from the left eye were processed and analyzed using custom Matlab scripts. Gaze data was pre-processed for two purposes: 1) to replace invalid data or data during blinks with last good values, and 2) to exclude invalid trials from analyses. Gaze data points were considered invalid if one or both eyes were not found or recorded gaze was outside the screen area. Blinks were detected by zero values for pupil diameter, as well as instantaneous rate of change of pupil diameter greater than approximately 0.05 mm/ms for both eyes. Trials were flagged as invalid for any of the following reasons: 1) more than 1000 ms of consecutive invalid gaze points after scene onset, 2) more than 1000 ms of consecutive invalid gaze points immediately prior to target location, or 3) more than 40% of invalid gaze points throughout the trial. On average, approximately 4% of trials were excluded using these criteria. Fixations were

calculated using a maximum velocity threshold of 75 degrees of visual angle/second, a dispersion threshold of 0.5 degrees of visual angle around the fixation centroid and a minimum duration threshold of 50 ms. Areas of Interest (AOIs) were hand drawn around distractors.

Statistical Analysis

Visual search

For accurate trials, two measures were extracted: search time and first look. Search time was calculated as the time from scene onset to click on target. First look indicated whether the first saccade and associated fixation after scene onset was to the distractor. First look was chosen in accordance with the previous literature, which suggested that fixations on distractors during visual search relate to incidental memory of distractors (Olejarczyk, Luke, & Henderson, 2014; C. C. Williams, Henderson, & Zacks, 2005), as well as increase search time (e.g., Boot, Kramer, & Peterson, 2005; Irwin, Colcombe, Kramer, & Hahn, 2000), and first fixations in particular indicate attentional capture in complex scenes (Becker, Pashler, & Lubin, 2007) as well as to faces specifically (Crouzet, Kirchner, & Thorpe, 2010).

Memory phase

To determine memory precision, memory error was evaluated as the distance in pixels from the accurate target location to the recalled location, for trials in which participants accurately found the target object at least once in the visual search task.

AIC modeling

For each dependent measure, two methods of statistical analysis were employed. The first was an information-theoretic (IT) approach using Akaike's information criterion (AIC) modeling (Burnham & Anderson, 2002). In this approach, a global linear mixed-effects model was created using all fixed predictor variables of interest, with subject and scene as random variables to account for the non-independence across trials within subjects and across blocks of the visual search task within scenes. Distractor was included as a random slope, to model potential individual differences in this variable of interest between subjects. First, the global model containing all fixed and random effects was specified. Next, a subset of candidate models that contained all possible combinations of the fixed effects included in the global model were specified. These candidate models were ranked according to their AIC score (lower scores indicate better fit), and the delta AIC (Δ_i) in relation to the highest-ranking model as well as the Akaike weight (w) were calculated using the *R* package *MuMIn* (Bartón, 2015). Akaike weight based averaging over all candidate models allowed for the derivation of three values to be used for analysis. First, the mean estimates of the coefficients (θ) were calculated by averaging the estimates over all candidate models that included the θ of interest, weighted by w . Second, for each θ of interest the 95% confidence intervals (CI) were calculated in order to determine which coefficients were statistically significantly different from zero. Finally, the 'Relative Influence' (RI) was calculated as the summation of w across all models that included the variable of interest, as a further indication of the importance of each predictor. Model averaging in this way accounts for model selection uncertainty by incorporating all possible models as opposed to comparing step-wise two models at a time (Burnham & Anderson, 2002). We used this approach to generate p -values, as opposed to the approach in the previous two chapters, due to the complexity of the models in the current chapter—the current models included

two random effects (subject and scene) as opposed to one in the previous chapters (subject).

The AIC modeling approach was used for four reasons: 1) to include all trials in the analyses as opposed to averaging over trials, which allows for incorporating the variance within subjects into the model, 2) to account for the variance between scenes, which more appropriately determines the strength of effects of the distractor on behavior over and above variability across scenes, also known in the literature as “controlling for item effects” (Baayen, Davidson, & Bates, 2008; Judd, Westfall, & Kenny, 2012), 3) to analyze proportion data appropriately by using logit linear mixed-effects models (Generalized Linear Mixed Effects Models for binomially distributed outcomes) with the binary response variable first look (Jaeger, 2008), and 4) to determine a priori if covariates should be included into further analyses. These additional analyses employed traditional repeated-measures ANOVA/ANCOVAs. This two-step method allowed us to investigate the direction of statistical relationships found in the AIC modeling approach. If any interaction term with the AQ or SAS as found to be significantly greater than zero using the AIC modeling approach, the AQ or SAS were included as covariates. In addition, G-power 3.1.9.2 (Faul et al., 2007) was employed to calculate statistical power for these traditional ANOVAs / ANCOVAs. Compromise power analyses (beta / alpha ratio = 4) showed that with $N = 37$, we achieved adequate power (71.5%) to detect a large ($f = 0.40$) sized main effect for a two-level within subject variable (e.g., distractor) or covariate (SAS or AQ), but less adequate power for three-level within-subject variables (e.g., block) (power = 64.5%) or power to detect medium (48.9%) sized effects.

All models were checked for the assumptions of normality and homogeneity of variance using visual inspection in *R*. If data were not normally distributed, data were

transformed with natural log (ln). The variable search time was transformed due to positive skew. The covariates AQ and SAS were centered and normed to allow for appropriate interpretation of main effects in the presence of significant interactions in the AIC modeling approach. There was a marginally significant correlation between the AQ and SAS, $r = 0.322$, $p = 0.052$. Finally, multicollinearity violations were checked, using variance inflation factor (VIF) values > 2 as a cut off. Where sphericity of the covariance matrix was rejected, Greenhouse & Geisser adjustments were used.

Results⁴

Visual search

Manual and eye-tracking measures provided converging evidence for social stimuli being more distracting than non-social stimuli, with the effects interacting with learning over successive blocks (see Table 12 for descriptives).

Table 12
Visual search descriptive statistics.

Distractor	Block	RT (s)	Accuracy (%)	First looks (%)
Social	1	4.85 (0.11)	97.09 (0.45)	26.49 (1.81)
	2	3.32 (0.06)	97.97 (0.34)	21.51 (1.39)
	3	2.60 (0.06)	98.31 (0.32)	18.60 (1.12)
Non-Social	1	5.00 (0.11)	95.95 (0.64)	16.97 (1.27)
	2	3.45 (0.07)	98.04 (0.33)	15.52 (1.23)
	3	2.53 (0.07)	98.12 (0.34)	14.11 (1.17)

Average values with standard errors in parentheses.

⁴ As we had four counterbalanced groups, we first ran analyses excluding one participant to allow for even numbers in each group. There were no differences in the results between this smaller sample and the full sample described below.

Search time (s)

We first investigated whether participants learned target locations across blocks, and whether distractor type affected this learning. Decreasing search time over blocks indicated learning and there was a moderating effect of distractor on learning slopes. AIC model averaging with manual response times during the visual search task revealed that the coefficient estimates for block as well as the distractor-by-block interaction term were significantly different from zero, indicating they had significant effects on the model (Table 13). A repeated-measures ANOVA with two within-subject factors (distractor: social, non-social; block: one, two, three), revealed a main effect of block, $F(1.47, 52.89) = 395.23, p < 0.001, \eta^2 = 0.92$, driven by decreasing search time across blocks. There was no main effect of distractor on search time, $F(1, 36) = 0.38, p > 0.250, \eta^2 = 0.01$, but there was a significant distractor-by-block interaction, $F(1.94, 69.98) = 3.78, p = 0.029, \eta^2 = 0.10$. Although Bonferroni-adjusted post-hoc tests revealed no significant differences in search time between social and non-social scenes in each block separately (block one: $p = 0.218$, block two: $p = 0.215$, block three: $p = 0.135$), and highly significant differences between blocks for both social and non-social scenes separately ($p < 0.001$), there was a significant interaction between distractor and block in the linear contrasts, $F(1, 36) = 5.13, p = 0.030, \eta^2 = 0.13$, suggesting a difference in slope across blocks between social and non-social scenes. Extracting the regression slopes for each participant for social and non-social scenes separately showed steeper negative slopes for non-social scenes ($M = -0.34 \ln(s), SD = 0.10 \ln(s)$) compared to social scenes ($M = -0.31 \ln(s), SD = 0.08 \ln(s)$) (Figure 11).

Table 13
Model averaging with parameters related to the dependent measures during visual search

Predictor	Search time (ln(s))			First Look (yes/no)		
	RI	θ	95% CI	RI	θ	95% CI
(Intercept)		1.461***	1.396		-1.908***	-2.207
Distractor	0.79	-0.021	-0.056	1	0.535***	0.229
Block	1	-0.619***	-0.655	1	-0.330*	-0.582
AQ	0.5	-0.024	-0.076	0.89	-0.159*	-0.300
SAS	0.55	-0.031	-0.082	0.67	0.100	0.227
Distractor x Block	0.68	0.054*	0.013	0.57	-0.301*	-0.002
Distractor x AQ	0.13	0.008	-0.016	0.44	0.155	0.388
Distractor x SAS	0.13	-0.004	-0.027	0.23	-0.094	0.145
Block x AQ	0.12	-0.012	-0.032	0.26	0.094	0.242
Block x SAS	0.13	0.013	-0.009	0.11	-0.030	0.119
Distractor x Block x AQ	0.01	-0.027	-0.068	0.03	0.207	0.497
Distractor x Block x SAS	<0.01	-0.015	-0.056	<0.01	-0.123	0.161

For each parameter and dependent measure, this table presents the relative influence (RI) (based on Akaike weights), the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI) based on estimated unconditional variance. Estimates with '***' differed statistically from zero based on 95% CIs with $p < 0.001$, '**' with $p < 0.01$, and '*' with $p < 0.05$. For both search time and first look, block had a significant effect, as would be predicted if learning took place. Distractor had a significant effect for first look, with more first looks to social distractors, as we would predict if social distractors in particular captured attention during search, even with distractors equated for salience. Furthermore, block-by-distractor interactions for both measures suggest differential distractor effects across blocks.

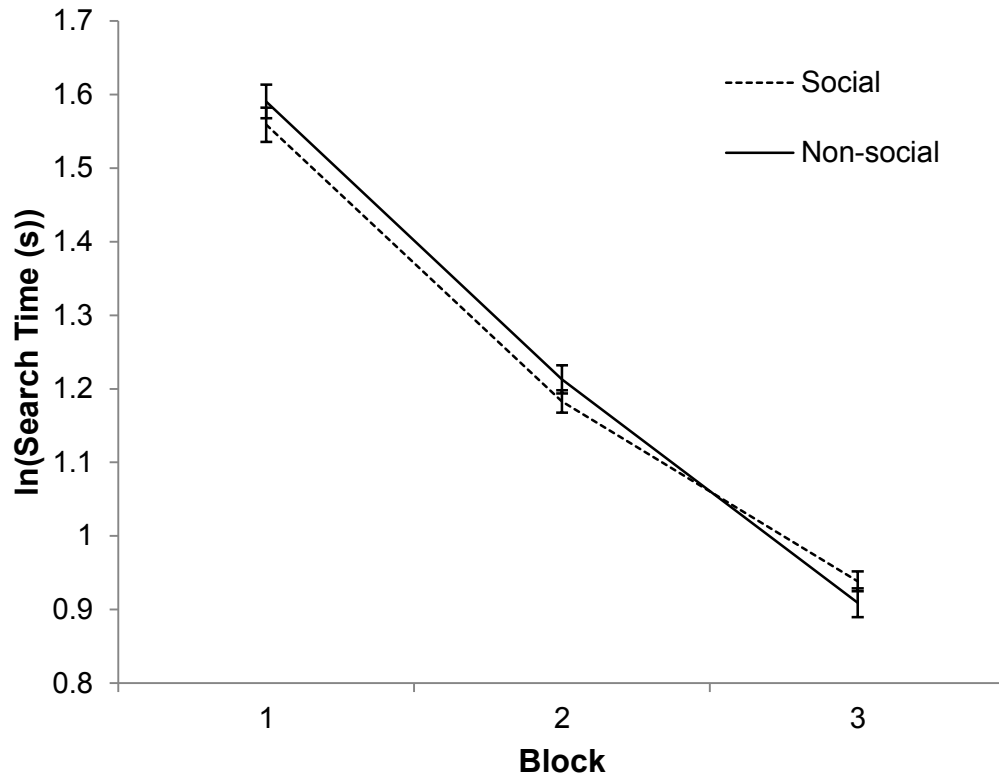


Figure 11. Interaction between block and distractor for visual search time. Although there were no significant differences between social and non-social scenes for each block separately, and there were highly significant differences between blocks for both social and non-social scenes separately, there was a significantly steeper slope across blocks for non-social compared to social scenes. Dotted line represents social trials and solid line represents non-social trials. Error bars are standard error of the mean (SEM).

First look (yes/no)

Next, to analyze whether distractor type predicted gaze behavior, we tested if the first saccade and subsequent fixation landed on the distractor (first look). There were more first looks to social distractors, indicating greater attentional capture, which decreased over blocks with a more negative slope for social scenes. In addition, overall attentional capture by both social and non-social distractors showed a negative

relationship with the AQ. For this analysis, logit mixed-effects models (Generalized Linear Mixed Effects Models for binomially distributed outcomes) were used in AIC modeling. Distractor, block, AQ, and the distractor-by-block interaction term had significant effects on the model (Table 13). The main effect of the AQ reflected the finding of a negative relationship between overall first looks, with fewer first looks for individuals with high autistic traits (Figure 12).

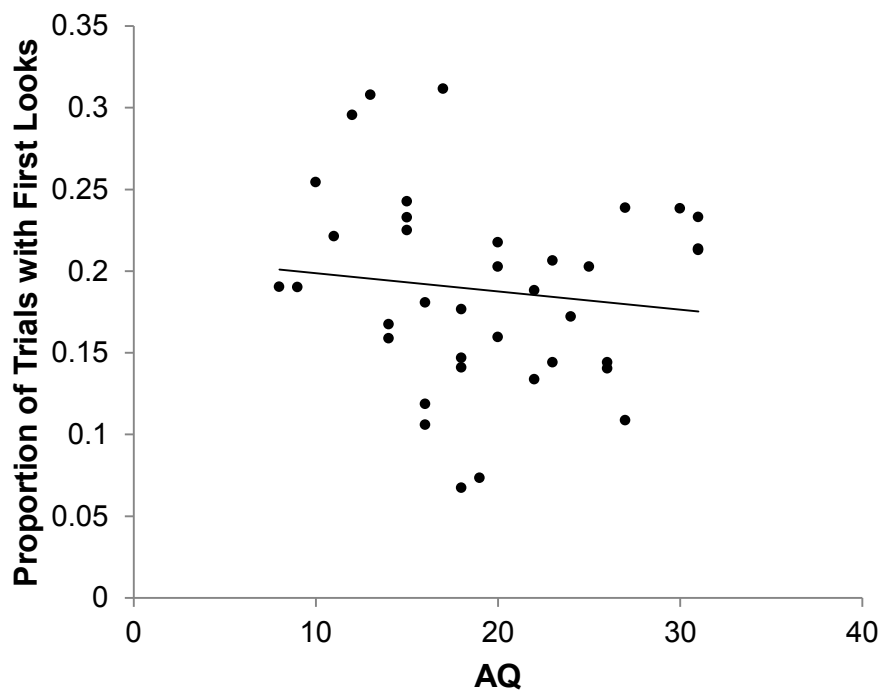


Figure 12. Depiction of the significant relationship between the AQ and first looks to distractors, with increasing scores on the AQ related to fewer first looks overall, regardless of whether the distractor was social or non-social.

A repeated-measures ANOVA with two within-subject factors (distractor: social, non-social; block: one, two, three), with proportion of trials with first looks as the dependent measure revealed a significant main effect of block, $F(1.77, 63.61) = 11.65$, $p < 0.001$, $\eta^2 = 0.24$, with first looks generally decreasing over blocks, a significant main

effect of distractor, $F(1, 36) = 14.17, p < 0.001, \eta^2 = 0.28$, with more first looks to social distractors (Figure 13), and a marginally significant distractor-by-block interaction, $F(1.77, 63.64) = 2.78, p = 0.068, \eta^2 = 0.08$.

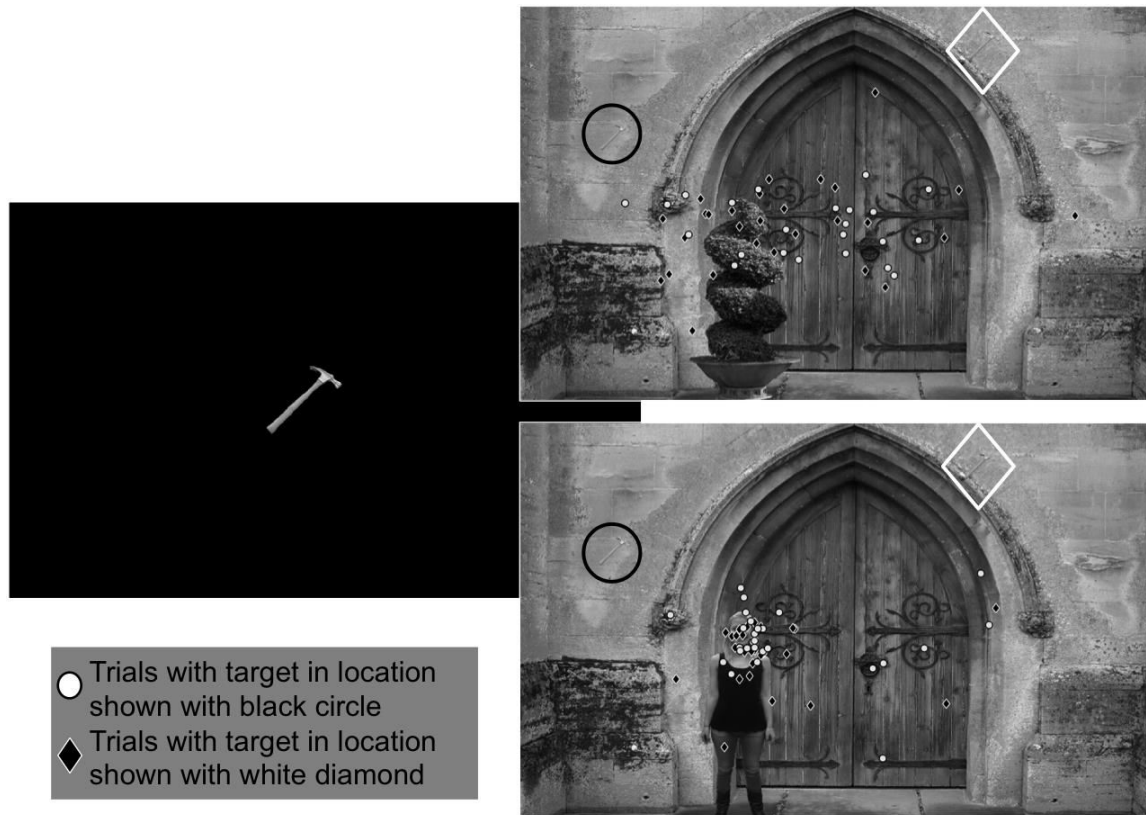


Figure 13. First looks during visual search for a representative scene. This figure depicts the between-subjects first looks across all three blocks for a representative scene. For some participants, the target appeared at the location marked with a black circle, and for some at the location marked with a white diamond. Regardless of the specific target location, participants looked at the social distractor more than the non-social distractor in the same scene, despite the fact that the two stimuli were equally salient with regards to low-level visual properties.

Although the interaction was only marginally significant, in light of the significant interaction term using the higher-powered AIC modeling approach, this interaction was followed up with post-hoc analyses. Bonferroni-corrected post-hoc tests revealed significant differences in first looks between social and non-social scenes for each block separately (block one: $p = 0.001$, block two: $p = 0.009$, block three: $p = 0.018$), but there was a significant interaction between distractor and block in the linear contrasts, $F(1, 36) = 4.55$, $p = 0.040$, $\eta^2 = 0.11$, suggesting a difference in slope in first looks across blocks between social and non-social scenes. Extracting the regression slopes for each participant for social and non-social scenes separately showed steeper negative slopes for social scenes ($M = -3.94\%$, $SD = 6.09\%$) compared to non-social scenes ($M = -1.43\%$, $SD = 3.94\%$).

Memory phase

Next, to investigate the effects of learning on memory performance, memory error (distance in pixels from recalled location to correct location) was analyzed. Participants showed poorer precision (higher error) for social compared to non-social scenes, and importantly this effect was moderated by the SAS with anxious individuals remembering target locations better under conditions of social distraction. AIC modeling revealed that the fixed-effects distractor and the distractor-by-SAS interaction terms had significant effects on the model (Table 14). In light of the significant interaction with the SAS, the SAS was included as a covariate in a repeated measures ANCOVA with one within-subject measures (distractor: social, non-social). There was a significant difference in memory error for target locations, $F(1, 35) = 15.00$, $p < 0.001$, $\eta^2 = 0.30$, with lower precision (higher error) for social compared to non-social scenes (social: $M = 179.60$, $SE = 7.10$; non-social: $M = 158.62$, $SE = 7.10$). There was also a

distractor-by-SAS interaction, $F(1, 35) = 10.04$, $p = 0.003$, $\eta^2 = 0.22$. Splitting the group by median SAS score shows this relationship to be driven by a significant difference in memory between social and non-social scenes for low SAS ($p = 0.005$) with lower precision (higher error) for social scenes, but no difference for high SAS ($p > 0.250$) (Figure 14).

Table 14

Model averaging with parameters related to memory error (pixels) during the memory phase.

Predictor	RI	θ	95% CI	
(Intercept)		158.529***	123.088	194.419
Distractor	0.98	20.537*	0.860	40.219
AQ	0.39	-8.521	-43.085	26.075
SAS	0.99	32.932	-2.191	66.564
Distractor x AQ	0.15	-11.015	-30.313	10.968
Distractor x SAS	0.9	-27.798**	-47.680	-7.915

For each parameter, this table presents the relative influence (RI) (based on Akaike weights), the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI) based on estimated unconditional variance. Estimates with '***' differed statistically from zero based on 95% CIs with $p < 0.001$, '**' with $p < 0.01$, and '*' with $p < 0.05$.

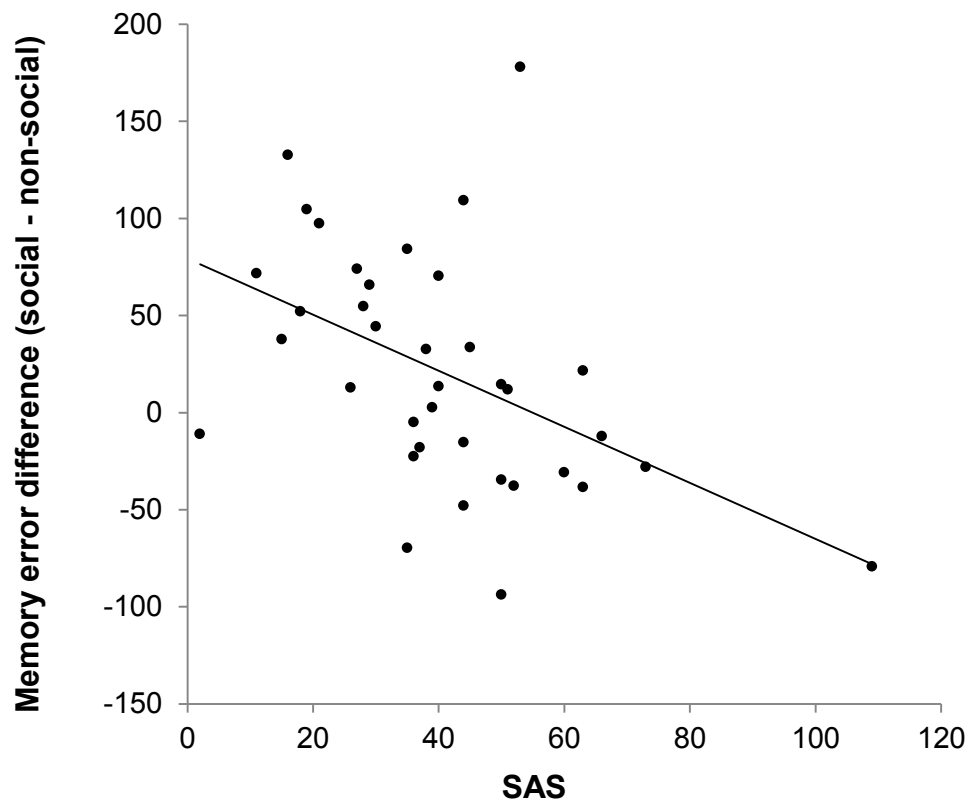


Figure 14. SAS vs. memory precision (error). Difference score between the average memory error (pixels away from target) for all social trials minus non-social trials during the memory phase versus SAS scores. Dots are individual participants. This graph depicts the significant distractor by SAS interaction. This relationship holds without the extreme SAS score, $F(1, 34) = 6.39, p = 0.016, \eta^2 = 0.16$.

To determine if we had sufficient power to detect this interaction with the SAS using mixed effects modeling, the *R* package *simr* (Green & MacLeod, 2016) was used, which calculates power for mixed effects models by simulation. An observed power analysis revealed 82.6% power based on 1000 simulations (CI: 80.11, 84.90).

Cross-measure relationships

In order to determine if there was a direct relationship between behavior during visual search and memory performance, we contrasted two potential candidate search indices during visual search as predictors of memory error: first-look proportion, as the proportion of the blocks (out of 3) in which the participant made a first look at the distractor for a particular scene; and search-time slope, as the regression slope of the search times across all three blocks for a particular scene. Both of these were entered as predictors for memory performance (error) for that particular scene, in addition to distractor type (Table 15). AIC model averaging revealed that search-time slope was highly predictive of memory performance, such that a shallower slope (as we found for social compared to non-social scenes) predicted poorer memory performance (higher memory error). Therefore, slope differences (i.e., improvements in speed to locate the target over blocks) are predictors of memory error.

Table 15

Model averaging relating visual search measures to memory error (pixels) during the memory phase

	RI	θ	95% CI	
(Intercept)		185.424***	147.786	223.105
First-look proportion	0.65	10.208	-5.04	25.425
Search-time slope	1	105.99***	65.918	146.113
Distractor	0.60	15.861	-9.074	40.613
First-look proportion x Search-time slope	0.18	-3.362	-46.928	39.801
First-look proportion x Distractor	0.11	-4.535	-28.865	19.947
Search-time slope x Distractor	0.16	4.651	-65.14	73.769
First-look proportion x Search-time slope x Distractor	<0.01	-9.584	-96.682	77.514

For each parameter, this table presents the relative influence (RI) (based on Akaike weights), the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI) based on estimated unconditional variance. Estimates with '***' differed statistically from zero based on 95% CIs with $p < 0.001$, '**' with $p < 0.01$, and '*' with $p < 0.05$.

Although gaze behavior overall (e.g., first-look proportion) was not predictive of memory performance, we explored whether gaze behavior influenced search time during visual search, and therefore perhaps indirectly affected memory. AIC model averaging revealed a three-way interaction between distractor, block, and first look (Table 16). To interpret this interaction, we performed AIC model averaging for social and non-social trials separately, using block and first look as predictors. We found that for social scenes, there was a main effect of first look, with longer search times when the social distractor was the first fixation, as well as a main effect of block. For non-social scenes, the main effect of first look was further qualified by an interaction between first look and block. These relationships are represented in Figure 15.

Table 16

Model averaging relating gaze behavior to search time in visual search

	RI	θ	95% CI	
(Intercept)		1.465***	1.399	1.532
Distractor	0.93	-0.030	-0.071	0.007
Block	1	-0.630***	-0.671	-0.591
First look	0.92	-0.018	-0.104	0.065
Distractor x Block	0.89	0.073**	0.021	0.125
First look x Block	0.58	0.107	-0.002	0.218
First look x Distractor	0.56	0.078	-0.018	0.177
Distractor x First look x Block	0.41	-0.158**	-0.267	-0.048

For each parameter, this table presents the relative influence (RI) (based on Akaike weights), the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI) based on estimated unconditional variance (see Supplementary Online Materials). Estimates with ‘***’ differed statistically from zero based on 95% CIs with $p < 0.001$, ‘**’ with $p < 0.01$, and ‘*’ with $p < 0.05$.

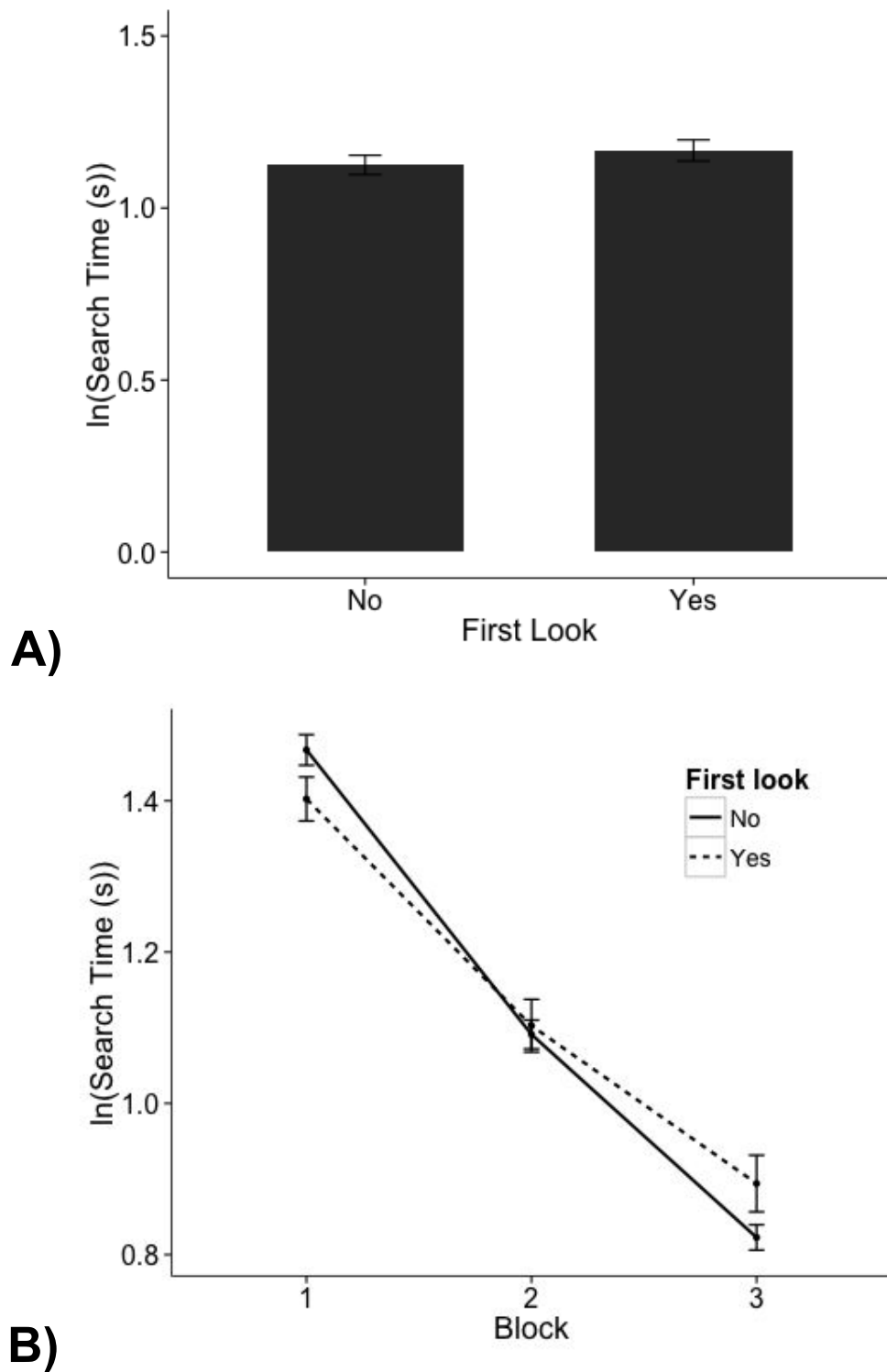


Figure 15. This figure depicts the significant main effect of first look when predicting search time for social scenes (A), and interaction between block and first look when predicting search time for non-social scenes (B). Error bars are SEMs.

An association between gaze behavior and search time and an association between search time and memory performance with a lack of a relationship between gaze behavior and memory performance suggest that search time may act as a mediating factor between gaze behavior and memory precision.

Discussion

This study aimed to investigate the functional consequences of social distraction on attention and memory, using complementary methodologies in cognitive science. First, using a novel task with greater ecological validity, our findings replicated the strong effects of social distraction on attention (Langton et al., 2008; Lavie et al., 2003; Riby et al., 2012), but critically, in our case, even when compared to distraction from items with similar low-level salience indexed by a computational algorithm (Harel et al., 2006). Eye-tracking showed greater attentional capture by social stimuli during visual search, consistent with previous findings (Crouzet et al., 2010). This effect was moderated by block, consistent with increasing control over attentional capture for social distractors, more so than for non-social distractors. Manual search time for targets also indicated that learning over blocks was moderated by distractor type, with a shallower learning slope for social scenes. Second, and to our knowledge for the first time, we showed that the effects of social distraction were not isolated to visual search, or even learning over time, but extended to subsequent memory for target locations with poorer memory precision for social scenes. Finally, social anxiety modulated memory precision, with better memory performance under social distraction for high-anxiety participants. In contrast, autistic traits did not moderate performance, but rather individuals with higher autistic traits demonstrated generally reduced attentional capture for both social *and* non-social distractors.

One exciting implication of this work is the extension of salience algorithms beyond predicting gaze behavior to investigating the functional consequences of visual salience. Salience algorithms are often used to predict eye movements, but only recently have these algorithms been used to predict memory performance, suggesting that target memory is correlated with target salience (Fine & Minnery, 2009; Santangelo & Macaluso, 2013). The current study extends this work by looking at the salience of *distracting* items in order to control for their potential effects on attention and memory, a needed and too infrequently used control, particularly for natural scenes.

Furthermore, this extended learning and memory paradigm allows us to go beyond visual search alone in testing the consequences of social distraction. Our findings support a relationship between distraction at encoding and poorer memory performance (Awh & Vogel, 2008; Foerde et al., 2006), but crucially demonstrate this effect in a novel way by utilizing attentional biases towards social stimuli often discussed in the literature (Langton & Bruce, 1999; Ro et al., 2001; Vuilleumier, 2000; Vuilleumier et al., 2001). Moreover, additional analyses reveal relationships among the dependent measures that suggest a possible mechanism of social distraction. Gaze behavior during visual search (i.e., proportion of first looks towards distractors, which we found to differ between social and non-social scenes, indicative of social distraction) predicted search slopes for locating targets over blocks. In turn, shallower search slopes during the visual search task (i.e., smaller improvements in speed to locate the target over blocks), predicted poorer memory performance. Importantly, we found shallower search slopes for social compared to non-social scenes. Although these analyses do not equate to a full mediation analysis, an association between gaze behavior during search and search speed on the one hand, and an association between search speed and memory performance on the other, with a lack of a direct relationship between gaze behavior and

memory performance suggests that search speed mediates the association between gaze behavior and memory precision.

The most novel findings are perhaps the effects of individual differences on social distraction. The finding that anxious individuals remember target locations better under conditions of social distraction may be surprising, as one might expect higher social anxiety to cause more distraction in social scenes and therefore poorer performance. Hypervigilance-avoidance in social anxiety accounts for these findings: social anxiety may be first characterized by hypervigilance to social stimuli, followed by avoidance (Vassilopoulos, 2005). Such avoidance may actually be advantageous in the current study, as people are distractors and not the targets of attention, and therefore may lead to better performance. The comparatively long presentation of social stimuli in our task compared to dot-probe tasks is likely to mean that participants will be in the avoidance phase; manipulating length of scene duration in the current study may validate the hypervigilance-avoidance hypothesis and reveal it to be a general as opposed to a spatial specific effect. Additionally, in clinical populations high social anxiety leads to poorer encoding of faces (Holsen, Dalton, Johnstone, & Davidson, 2008). Individuals with high anxiety in this study may therefore not encode as much distracting information about the people, which in turn might allow for better memory for target locations in social scenes. Importantly, our current sample was only adequately powered to detect large sized effects of either individual differences in social anxiety or autism traits (see below) and therefore requires further investigation.

In addition, although we did not observe an interaction with autism traits as we had expected, a main effect of AQ for first looks is important in the context of the current thesis. Although many studies conclude that autistic individuals show less attentional capture to social stimuli, these studies do not often directly compare attention

to social stimuli to attention to well-controlled non-social stimuli. Aside from social impairments, autistic individuals demonstrate low-level perceptual differences with regards to color and contrast, as described in Chapter 1 (Bertone, 2005; Franklin et al., 2010; S. Wang et al., 2015). It is possible that, compared to non-social objects equated for visual salience, autistic individuals do prefer social stimuli, but demonstrate reduced attention to salient stimuli in general driven by perceptual differences. This may explain discrepancies between some studies that find differences in social attention and others that do not (Fischer, Koldewyn, Jiang, & Kanwisher, 2013), as these studies often do not control for the salience characteristics of natural stimuli. Our results are consistent with this hypothesis, and emphasize the need for well-controlled comparison stimuli for making appropriate conclusions when investigating social attention biases. However, caution is warranted not only because of the aforementioned statistical power consideration, but also because we investigated individual variation in a neurotypical population and not individuals with a full ASD diagnosis. In addition, although SAS and AQ scores did not correlate in our sample, social anxiety and ASD are highly comorbid in clinical samples (Bellini, 2006), and therefore determining the contributions of one independent of the other may be more difficult to do with diagnosed autistic individuals. This again complicates inferring directionality in the context of ASD, leaving the debate on hypersensitivity to social stimuli in social anxiety versus hyposensitivity in ASD open to further investigation (Senju & Johnson, 2009).

This work builds on the previous attentional bias literature. Our study suggests that encounters with distracting social stimuli affect not just the here and now, but the subsequent memories built from perceptual/learning interactions. More importantly, this effect is modulated by individual differences in sensitivity to social stimuli. Attentional biases therefore not only operate in a selective attention domain, but also have

functional consequences on memory, which may in turn reinforce these biases. This idea has far-reaching implications in psychopathology, from anxiety to depression to autism. Attentional biases are often implicated in these disorders, yet until now the functional consequences of such biases on other aspects of cognition have not been investigated.

Importantly for the current thesis, the findings here reveal a possible mechanism by which an atypical social attention bias may operate in ASD to affect social functioning. If a neurotypical attention bias towards social stimuli affects memory for the non-social, task relevant information in the current study, it is possible that an attention bias *away* from people (or more appropriately a reduced social attention bias), as is often described by ASD researchers, may result in poorer learning and memory for social stimuli. Over time, a lack of knowledge about people and the social world may result in the social impairments that are so prominent in ASD. The current study is therefore only preliminary evidence—a similar paradigm should be investigated with diagnosed ASD individuals for more concrete evidence of this mechanism.

Chapter 5: The functional consequences of social attention/inattention:

Memory-guided attention orienting and neural markers

Candidate contribution: The candidate significantly contributed to every stage of this study, including: experimental design and implementation, recruitment, data collection, analysis strategy, data analysis, and written report.

Introduction

Chapter 4 suggested that there are indeed functional consequences of social distraction on learning and memory. Both behavioral and gaze differences occurred during visual search that were indicative of social distraction, and these behavioral differences were associated with subsequent poorer memory performance for target locations in social scenes. However, in addition to attention affecting memory performance, memory performance also affects attentional orienting, a bidirectional relationship that is well-documented for both short-term (Astle & Scerif, 2011; Griffin & Nobre, 2003; Kuhl & Chun, 2014) and longer term memory (Chun & Turk-Browne, 2007; Goldfarb, Chun, & Phelps, 2016; Hutchinson & Turk-Browne, 2012; Rosen, Stern, Michalka, Devaney, & Somers, 2016). It is possible that the effect of social distraction on learning and memory may in turn alter later orienting within natural scenes, completing the bidirectional chain. In addition, what are the neural markers of social distraction in relation to this novel memory-guided attentional orienting aspect?

There is ample evidence for the fact that learning and memory guides attentional orienting. For example, the contextual cueing literature suggests that implicit memories for simple visual search arrays that have been previously seen facilitate performance by reducing visual search time compared to novel search arrays (Chun & Jiang, 1998).

Other, more recent work has built on these studies by reporting that spatial, contextual long-term memories for objects located within natural scenes also enhance perceptual sensitivity and response time for detecting objects occurring within learned scene locations during subsequent attention-orienting tasks (Patai et al., 2012; Patai, Buckley, & Nobre, 2013; Stokes, Atherton, Patai, & Nobre, 2012b; Summerfield, Lepsien, Gitelman, Mesulam, & Nobre, 2006; Summerfield, Rao, Garside, & Nobre, 2011). In these tasks, participants search for target objects in natural scenes over several blocks, to form a memory for where the target is located in each scene, similar to the study in Chapter 4. Memory precision for target location is also tested. After a break, participants engage in a covert orienting task. In one version, participants must react to the onset of the target superimposed on a previously studied scene in either the learned location (valid trials) or in a different location (invalid trials) while fixating centrally (Salvato, Patai, & Nobre, 2016a; Salvato, Patai, McCloud, & Nobre, 2016b; Summerfield et al., 2006). This classic memory-based Posner-style cuing paradigm leads to a validity effect, whereby reaction time (RT) for invalid trials is significantly longer than for valid trials. This additional orienting task therefore allows for investigating the effects of memory on attention orienting. Hence, it can be classified as a memory-guided orienting task akin to contextual cuing. As we have shown that social distraction affects memory performance, it is possible that this memory difference will subsequently affect attentional orienting.

Furthermore, can the effects of social distraction on memory-guided attention orienting be seen in neural activity? In the current task we utilize natural social and non-social distractors embedded within scenes – human figures or objects with similar physical salience (the same as in Chapter 4). Are there neural markers that signify the difference between these conditions? One distinctive neural marker for social stimuli

that may be relevant is the N170 event-related brain potential (ERP) elicited by face stimuli. The N170 is a large negative potential distributed over lateral posterior electrodes with a latency of approximately 140-200 ms post-stimulus, strongly linked to the structural encoding of faces (Eimer, 2000b). Although the vast majority of the N170 studies use centrally presented faces, more recent studies have also investigated neural activity to laterally presented faces. More specifically, Towler and Eimer (2015) have reported that the N170 is elicited exclusively at posterior electrodes contralateral to laterally presented face stimuli. However, the stimuli used by Towler and Eimer, as well as the majority of the N170 literature, are isolated faces presented out of context (see Righart & de Gelder, 2006; Rousselet, Macé, & Fabre-Thorpe, 2004a; 2004b for examples of central faces in natural scenes). The contralateral nature of the N170 has not been investigated using more natural social stimuli. As the current study investigates social distraction using social stimuli embedded in natural scenes at lateral locations, it is possible to investigate this novel question.

Another approach to investigating the effect of social distraction at the neural level is examining preparatory activity triggered by memory. Both explicit perceptual cues (e.g., Romei, Gross, & Thut, 2010; Worden, Foxe, Wang, & Simpson, 2000) as well as mnemonic cues for memory-guided orienting in natural scenes (Stokes, Atherton, Patai, & Nobre, 2012a; Summerfield et al., 2011) induce preparatory desynchronization of neural oscillations in the alpha range (8-12 Hz) in posterior electrodes contralateral relative to ipsilateral to the cued location. As alpha lateralization has been reported to correlate with changes in neural excitability (Jensen & Mazaheri, 2010; Kelly, Lalor, Reilly, & Foxe, 2006), it is argued that alpha desynchronization occurs to allow increased processing of stimuli in a particular spatial location (Stokes, Atherton, Patai, & Nobre, 2012a).

Chapter 4 revealed explicit memory to be poorer for target locations in social scenes compared to non-social scenes. Thus it would be interesting to test whether the orienting of attention linked to the acquisition of such explicit memory measures would show diminution of alpha desynchronization.

The current study therefore sought to address two broad aims. The first aim explores the functional consequences of social distraction during learning on behavioral markers of attention: will poorer explicit memory for social scenes after a visual search task affect memory-guided attention orienting in a Posner-like cueing task? The second aim of the current study is to identify possible neural markers of social distraction during memory-guided attention orienting. Will the lateralized embodied faces in natural scenes elicit an N170 potential? Additionally, what are the neural consequences of social distraction on memory-related preparatory activity? Will differential memory performance between social and non-social scenes be detected in preparatory alpha desynchronization contralateral to target locations held in memory, in anticipation of target stimuli?

Methods and materials

Participants

The University of Oxford Central University Research Ethics Committee (CUREC) approved this research. Twenty healthy adult volunteers participated. All had normal or corrected-to-normal vision. Two participants were excluded due to inability to record EEG. The final sample consisted of eighteen participants aged 19-21, 15 female. Participants were recruited through a lab practical for undergraduate psychology students at the University of Oxford. All participants provided written informed consent and received course credit for their participation.

Stimuli

Stimuli were the same as those used in the previous study in Chapter 4. Stimuli were also similarly counterbalanced across participants, with one additional counterbalance. Target location and distractor type remained counterbalanced, while validity of the scene during the orienting phase (described below) was additionally counterbalanced. While half saw the same 40 scenes as valid and the other 40 scenes as invalid, the other half of the participants saw the reverse. Within this counterbalancing, distractor location (left or right side) and gender of social distractors (male or female) were also balanced to the extent possible (Figure 16). Target location (same or opposite side as distractor), distractor location (left or right side), and validity (valid or invalid scene during the orienting phase) counterbalancing resulted in eight participant groups.

Distractor type	40 social												40 non-social			
Distractor location	20 left				20 right				20 left				20 right			
Target location	10 same		10 opp		10 same		10 opp		10 same		10 opp		10 same		10 opp	
Validity	5V	5I	5V	5I	5V	5I	5V	5I	5V	5I	5V	5I	5V	5I	5V	5I
Distractor gender	3 M	2 F	2 M	3 F	2 M	3 F	2 M	3 F	2 M	3 F	2 M	3 F	2 M	3 F	2 M	3 F
Not applicable																

Figure 16. Scenes balanced for distractor type, distractor location, target location, orienting phase validity and distractor gender. Distractor location refers to screen hemifield. Target location is with respect to the distractor: same or opposite (opp) side of the distractor. Validity is with respect to the target appearance during the orienting phase: valid (V) or invalid (I) location. Distractor gender (F: female, M: male) is only applicable to social scenes.

Procedure

Visual search

Participants sat 60 cm away from a 23" 1920 by 1080 resolution monitor (spanning 45.89 by 26.90 degrees of visual angle). Instructions and task structure were the same as the previous study in Chapter 4 with several small adjustments. Instead of pressing the spacebar to reveal the cursor, participants pressed the mouse. Because a higher resolution monitor was used for this task, the scenes were displayed centrally using the resolution of the previous study (1680 by 1050) with a grey (153, 153, 153) border surrounding. A practice phase was included before the task, consisting of twelve trials. The task was themed after the movie "Despicable Me," including images of the characters during the feedback and instruction screens, a story for the task including the characters to make the task appear more like a game, and points acquired after each block (which were random and increasing from block to block). When the targets were correctly located, they flashed bigger and smaller for positive reinforcement. These last three alterations were included to make the task child-friendly for compatibility with subsequent developmental experiments (Chapter 6). The child-friendly version was used with adults here for consistency and to enable comparisons between age groups.

The current study used a Tobii TX300 eye-tracker with gaze recorded from both eyes at 300 Hz following a 9-point calibration. This eye-tracker was used as it allows for greater head movement and does not require a chin rest, which is more practical and better suited for children. Participants' eye gaze positions were calibrated before the start of each block.

Memory phase

This phase was identical to the previous study, but also included a “Despicable Me” themed introduction.

Orienting phase

After the memory phase, participants were capped for EEG, which lasted approximately 30 minutes. Participants then engaged in a memory-guided orienting task in which they reacted to the brief appearance of targets within their associated scenes. This task was a covert orienting task—participants were required to hold their gaze at a centrally located fixation cross present during the entire presentation of scenes.

Trials commenced with the presentation of a the central target (2.16 by 2.16 degrees of visual angle) for 3000 ms. The scene appeared after a fixation cross on a blank screen for 500-1500 ms. The target object was presented superimposed on the scene for 100 ms after 1000-1500 ms. After target disappearance, the scene remained present for 1000 ms during a response window. A fixation point remained present throughout the trial (Figure 17). After each trial, a blank screen appeared for 1500 ms, during which participants could blink, followed by the presentation of fixation square lasting between 1000-1500 ms, which prompted participants to get ready to the next trial. Participants responded to the presentation of the target object by pressing the left mouse button if the target appeared on the left and the right mouse button if the target appeared on the right. Although several previous studies using this memory-guided orienting task utilized a presence/absence version of the orienting task in which entire scenes were presented briefly (200ms) (e.g., Patai et al., 2012), this version was chosen for being simpler for use with children in subsequent experiments (Chapter 6). In half the scenes, the object appeared in the learned location (valid trials) and in the other half the object appeared in a new location on the opposite hemisphere (invalid trials).

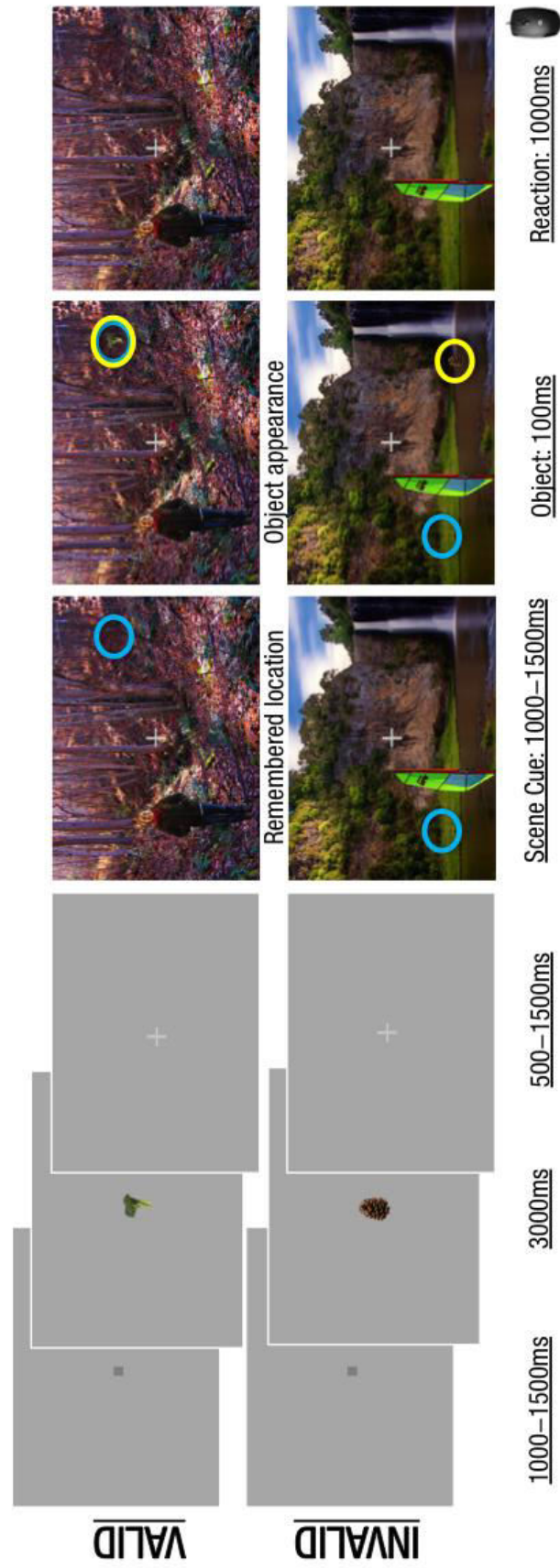


Figure 17. Trial sequence for the orienting phase. Participants viewed: 1) a fixation square, 2) the centrally presented target, 3) a warning cross, 4) the scene cue, 5) the target appearance, 6) reaction time window.

At the start of EEG testing, participants were instructed to blink as little as possible, to avoid making saccades, and to move their heads as little as possible. Participants were then allowed 12 practice trials to make sure they understood the task. To encourage fewer blinks during each trial, participants were instructed to blink during the blank screen that preceded the appearance of the fixation square. To reduce fatigue, participants had a short break every 16 trials. The entire orienting task, including practice trials, lasted approximately 15 minutes.

Follow-up

One particular concern with the study design was that any differences in behavior during the orienting phase could be due to the presence of distracting social stimuli at retrieval, and not necessarily due to any differences in memory encoding. For this reason, participants were followed up during a subsequent lab practical, on average 14.33 days after they were first tested with a range of 8-20 days (“timepoint two”). This wide range was due to their first visit data being collected over a two-week period. In this follow-up, participants first performed the memory phase for a second time. The procedure was identical to that in the first visit (“timepoint one”). Participants then engaged in the orienting phase for a second time, which was identical to the first visit except that a blank gray screen was presented instead of the scene during the scene cue, object appearance, and reaction period (Figure 17). Only the initial central presentation of the target object cued the spatial contextual memory for the subsequent target location. Target objects then appeared in the same valid and invalid locations as previously, as if the scenes had been present. Although the order of scene presentation was randomized for the orienting phase at timepoint two, it was identical to timepoint

one with regards to counterbalancing for each participant (scenes that were valid at timepoint one were also valid at timepoint two).

EEG acquisition and processing

EEG activity was recorded using a 128-channel Hydrocel Geodesic Sensor Net connected to Net Amps 300 (Electrical Geodesics Inc., Eugene, OR, USA) using NetStation 4.5 software. EEG signal was referenced online to the vertex and was sampled at 250 Hz. Electrode impedances were kept below 50 k Ω as recommended by the manufacturer. Eye movements and eye blinks were monitored with six eye channels placed on the outer canthi of both eyes and above and below the eyes. EEG processing was conducted using Fieldtrip software (Donders Institute for Brain, Cognition and Behavior). EEG data were filtered offline with band-pass filter 0.1–30 Hz, re-referenced to the average reference, and segmented into two time epochs.

Two types of epochs were segmented from the continuous EEG stream, to analyze ERPs elicited by the scene cues and the induced preparatory oscillatory activity.

Epochs for ERP analysis began 200 ms before and ended 500 ms after the presentation of the scene cue. Trials with artifacts were excluded after visual inspection. In particular, trials with EOG deflections exceeding ± 50 μ V, suggestive of blinks or saccades, or any electrode exceeding ± 100 μ V, suggestive of excessive drift, were excluded. All participants had at least 20 clean trials per condition (out of 40) after this process (social: $M = 30.78$, non-social: $M = 29.94$). ERP data were baseline corrected using the 200-ms pre-stimulus interval.

Longer epochs were used for analysis of alpha oscillations. These began 750 ms before and ended 4500 ms after the presentation of the central target. This long epoch was to allow for as many cycles as possible in estimating alpha oscillation power. Due

to the long epoch, which resulted in more frequent blinks, ICA was utilized for removing artifactual components from the data. Trials with muscle artifacts (identified with frequency in the 110-120 Hz range pre-filtering) and jumps were removed prior to ICA. Bad channels, identified via visual inspection, were not included in the ICA and were interpolated after artifactual components were removed from the data. Visual inspection was then conducted to remove trials that still contained artifacts after component removal. All participants had at least 20 clean trials per condition (out of 40) after this process (social: $M = 22.39$, non-social: $M = 22.94$). Time-frequency analysis was performed using a multitaper method with a Hanning taper and frequency-dependent window length encompassing four cycles. The resulting power spectra were baseline corrected using a relative baseline (percent change from baseline for each frequency) and a 200 ms pre-stimulus interval.

To investigate ERPs and alpha oscillations contralateral compared to ipsilateral to learned target locations as well as social/non-social distractors, channels from trials in which stimuli were on the left hemisphere were flipped to make all trials appear as if stimuli were on the right. In this way, contralateral electrodes could be easily compared to ipsilateral electrodes by comparing the left hemisphere of electrodes (contralateral) to the right hemisphere of electrodes (ipsilateral).

Eye-tracking processing

Processing was performed in the same manner as the previous study, Chapter 4.

Statistical analysis

Visual search

The measures used in the current study were the same as for the previous study in Chapter 4: Search time from scene onset to click on target (s) and first look (whether the first saccade and associated fixation after scene onset was to the distractor), were both calculated only for trials in which the target was accurately located. Accuracy was calculated as whether participants correctly clicked on the target within a 0.63 degrees of visual angle buffer.

Memory phase

Memory error was measured as in the previous study: distance in pixels from the accurate target location to recalled location, for trials in which participants accurately found the target object at least once in the visual search task.

Orienting phase

Accuracy was calculated as trials in which participants correctly responded to the location of the target appearance (on the left or right hemisphere) with the left or right mouse button within the reaction-time window. Reaction time from target onset to mouse press was calculated for accurate trials. Included trials for reaction-time analyses were also limited to trials in which participants accurately found the target object at least once during the visual search task, and trials in which the reaction time was within two standard deviations of the mean for that condition for that participant.

AIC modeling

For each dependent measure, model averaging was performed following the procedure outlined in the previous chapter. Random slopes were included in the mixed-effects models according to the “best-path” method described in the literature (Barr,

Levy, Scheepers, & Tily, 2013). All models were checked for the assumptions of normality and homogeneity of variance using visual inspection in R. If data were not normally distributed, data were transformed with natural log (ln). The variable search time was transformed due to positive skew.

EEG analyses

Cluster-based permutation tests were conducted using Fieldtrip software. For analyses investigating activity contralateral compared to ipsilateral electrodes, differences between homologous electrodes on either hemisphere were compared, reducing the number of observations in the cluster analysis by half.

Results

Visual search

We analyzed both search time and first look during the visual search task, to determine if the effects found in Chapter 4 were replicated in the current study.

Accuracy (%)

Accuracy was at ceiling, with no significant effects other than the intercept when using model averaging (results not shown) (social block 1: M = 97.88%, SD = 3.79%; social block 2: M = 98.31%, SD = 1.96%; social block 3: M = 98.75%, SD = 2.26%; non-social block 1: M = 97.78%, SD = 2.43%; non-social block 2: M = 98.06%, SD = 2.24%; non-social block 3: M = 98.19%, SD = 2.32%).

Search time (s)

AIC model averaging with search time during the visual search task revealed that the coefficient estimates for block as well as for the interaction between distractor and block were significantly different from zero, indicating their significant effects on the model (Table 17). A repeated-measures ANOVA with two within-subjects factors (distractor: social, non-social; block: one, two, three) revealed a main effect of block, $F(1.50, 25.46) = 189.21, p < 0.001, \eta^2 = 0.92$. There was no interaction between distractor and block, $F(1.87, 31.87) = 2.13, p = 0.138, \eta^2 = 0.11$. However, the linear contrasts were marginally significant, $F(1, 17) = 2.13, p = 0.078, \eta^2 = 0.17$. In light of the significant effect of the distractor-by-block interaction term in model averaging as well as the smaller sample size compared to Chapter 4, investigating the slopes in a similar manner to Chapter 4 revealed shallower search slopes for social compared to non-social scenes (Figure 18).

Table 17
Model averaging with parameters related to the dependent measures during visual search

Predictor	Estimate	Search time (ln(s))			Estimate	First look (yes/no)		
		I-95% CI	u-95% CI	p-value		I-95% CI	u-95% CI	p-value
(Intercept)	1.206	1.094	1.321	<0.001	-1.818	-2.157	-1.475	<0.001
Block	-0.538	-0.623	-0.459	<0.001	-0.195	-0.528	0.138	0.251
Distractor	-0.015	-0.061	0.012	0.495	0.26	-0.225	0.761	0.305
Distractor x Block	0.063	0.011	0.115	0.017	-0.548	-0.972	-0.124	0.011

For each parameter and dependent measure, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

First look (yes/no)

Due to the binary nature of the dependent measure, logit mixed-effects models (Generalized Linear Mixed Effects Models for binomially distributed outcomes) were used in AIC modeling. The only fixed-effect coefficient that was significantly different from zero was the interaction between distractor and block. A repeated-measures ANOVA with two within subjects factors (distractor: social, non-social; block: one, two,

three) using the proportion of trials with a first look as the dependent measure revealed a marginally significant effect of block, $F(1.73, 29.38) = 2.87$, $p = 0.08$, $\eta^2 = 0.14$. There was also a distractor-by-block interaction, $F(1.68, 28.52) = 5.21$, $p = 0.02$, $\eta^2 = 0.23$. Post-hoc analyses revealed this interaction to be driven by significantly higher proportion of first looks to social compared to non-social distractors in block one ($p = 0.047$), but no significant differences in blocks two and three ($p > 0.250$) (Figure 18).

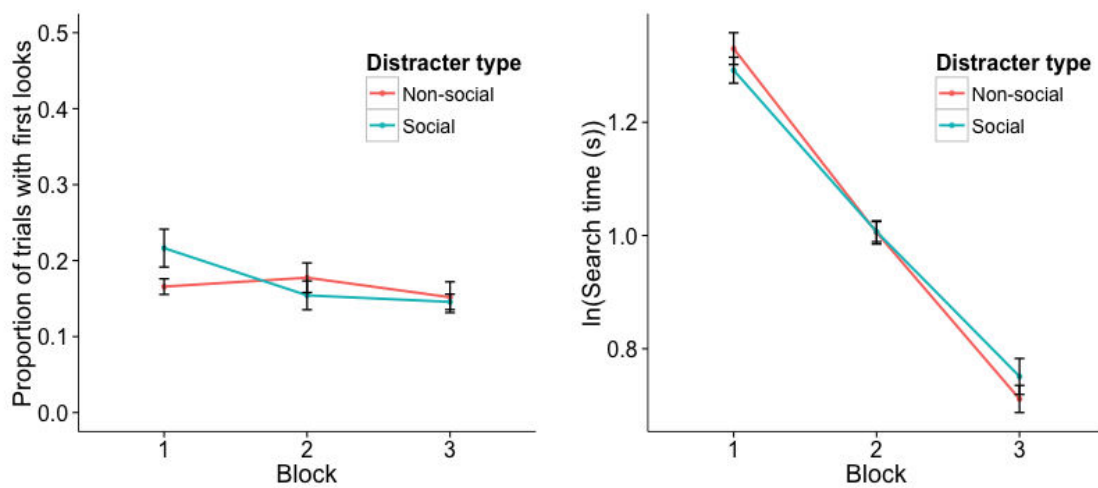


Figure 18. Mean proportion of trials with first looks and search times for social and non-social scenes over three blocks during visual search. Error bars are standard error of the means (SEMs). Participants made more first looks towards social distractors compared to non-social distractors in block one, but not blocks two and three. Participants also had shallower search time slopes over three blocks for social scenes compared to non-social scenes.

Memory phase

In order to determine if the poorer memory for social scenes from the previous study replicated with our EEG participants, memory error (distance in pixels from recalled to correct location) was analyzed. AIC modeling revealed a significant effect of

distractor (estimate = 12.63, $p = 0.028$, no CIs due to only having one fixed effect: distractor), with poorer memory (larger error) for social scenes (social: $M = 185.57$, $SD = 26.18$, non-social: $M = 158.56$, $SD = 26.18$), similar to the previous study. Similarly, a repeated-measures ANOVA with one within-subjects factor (distractor: social, non-social) revealed a main effect of distractor type, $F(1, 17) = 9.58$, $p = 0.007$, $\eta^2 = 0.36$.

Orienting phase

Accuracy (%)

Accuracy was at ceiling, with no effects other than a significant coefficient for the intercept (results not shown) (social valid: $M = 97.59\%$, $SD = 1.96\%$; social invalid: $M = 98.18\%$, $SD = 2.37\%$; non-social valid: $M = 98.57\%$, $SD = 1.98\%$; non-social invalid: $M = 98.85\%$, $SD = 2.52\%$).

RT (s)

Model averaging using RT during the orienting phase showed a significant effect of all three fixed effects: distractor, validity, and the distractor-by-validity interaction (Table 18). A repeated-measures ANOVA with two within-subjects variables (distractor: social, non-social; validity: valid, invalid) revealed a main effect of validity, $F(1, 17) = 45.54$, $p < 0.001$, $\eta^2 = 0.73$. There was also a marginally significant distractor-by-validity interaction, $F(1, 17) = 4.33$, $p = 0.053$, $\eta^2 = 0.20$. In light of the significant interaction from model averaging, the distractor-by-validity interaction was followed up with subject average post-hoc analyses, which revealed this interaction to be driven by significantly longer RTs for invalid social trials compared to invalid non-social trials ($p = 0.030$), but no difference between social and non-social scenes for valid trials ($p > 0.250$) (Figure 19).

Table 18

Model averaging with parameters relevant for orienting phase RT (s)

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	0.394	0.37	0.418	<0.001
Distractor	0.015	0.005	0.026	0.012
Validity	-0.03	-0.041	-0.018	<0.001
Distractor x Validity	-0.021	-0.036	-0.006	0.006

For each parameter, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

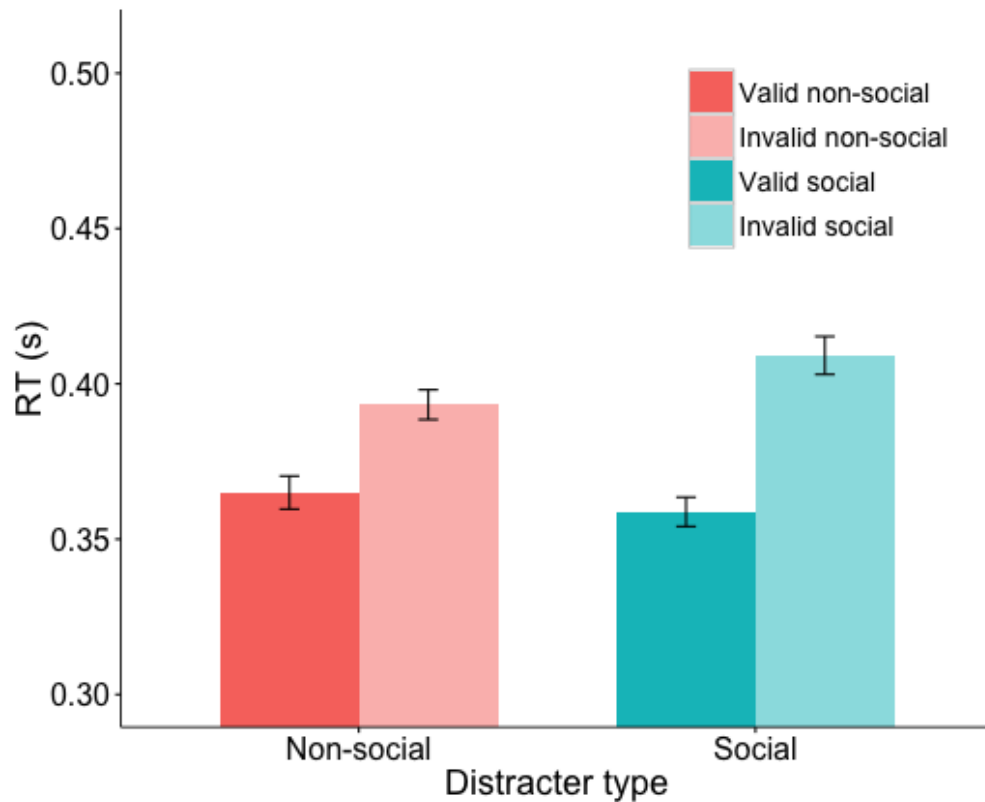


Figure 19. Mean RTs during the orienting phase demonstrate an overall validity effect for both social and non-social scenes, with slower RTs for invalid compared to valid trials, while also showing a moderating effect of distractor type with slower RTs for invalid social trials compared to invalid non-social trials. Error bars are SEMs.

Cross-measure relationships

Visual search, search time (s)

To investigate whether gaze behavior towards distractors predicted search time during the visual-search task, we used a similar procedure to that in Chapter 4. First look, distractor, and block, as well as all possible interactions between these variables, were entered as predictors for search time in AIC model averaging. Apart from the effects described above, there was only a marginally significant interaction between first look and distractor ($p = 0.056$), and no other effects including first look ($p > 0.250$) (results not shown here).

Memory phase, memory error (pixels)

To investigate whether gaze behavior or search slope during the visual search task predicted memory error during the memory phase, search-time slope (the regression slope of the search times across all three blocks for a particular scene), first-look proportion (the proportion of the blocks out of three in which the participant made a first look at the distractor for a particular scene), and distractor were entered as predictors for memory error in model averaging. In addition to the effects seen in the above memory phase analyses, there was a significant effect of search-time slope, with shallower slopes associated with poorer memory precision (higher error), similar to participants in Chapter 4 (Table 19).

Table 19

Visual search measures (search-time slope and first-look proportion) as predictors for memory error during the memory phase

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	154.591	110.313	197.809	<0.001
Search-time slope	25.654	4.098	46.798	0.019
Distractor	31.186	3.246	59.126	0.029
Distractor x Search-time slope	23.717	-4.624	52.093	0.101
First-look proportion	12.339	-6.441	31.247	0.198
Distractor x First-look proportion	-17.81	-46.367	10.704	0.221
First-look proportion x Search-time slope	-2.743	-16.465	10.465	0.701
First-look proportion x Search-time slope x Distractor	-5.887	-32.927	21.153	0.67

For each parameter, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

Orienting phase, RT (s)

To investigate whether memory precision during the memory phase subsequently predicted RTs in the orienting phase, memory error, distractor, validity, and all interactions between these variables were entered as fixed effects in AIC model averaging. In addition to the effects described above, there was also a significant effect on the model of the interaction between memory error and validity (Table 20). Following up on this interaction, post-hoc analyses with subject averages revealed that, while there was a significant positive correlation between memory error and RT for valid trials during orienting ($r = 0.52$, $p = 0.027$), with worse memory precision related to longer RTs, there was no significant correlation for invalid trials ($r = 0.15$, $p > 0.250$) (Figure 20).

Table 20

Memory error (pixels) during the memory phase as a predictor for orienting phase RT

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	0.395	0.371	0.418	<0.001
Memory error	-0.003	-0.011	0.005	0.538
Distractor	0.016	0.005	0.027	0.01
Validity	-0.03	-0.041	-0.018	<0.001
Memory error x distractor	-0.007	-0.017	0.004	0.199
Memory error x validity	0.015	0.004	0.025	0.006
Distractor x validity	-0.025	-0.042	-0.009	0.002
Memory error x distractor x validity	-0.007	-0.024	0.01	0.426

For each parameter, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

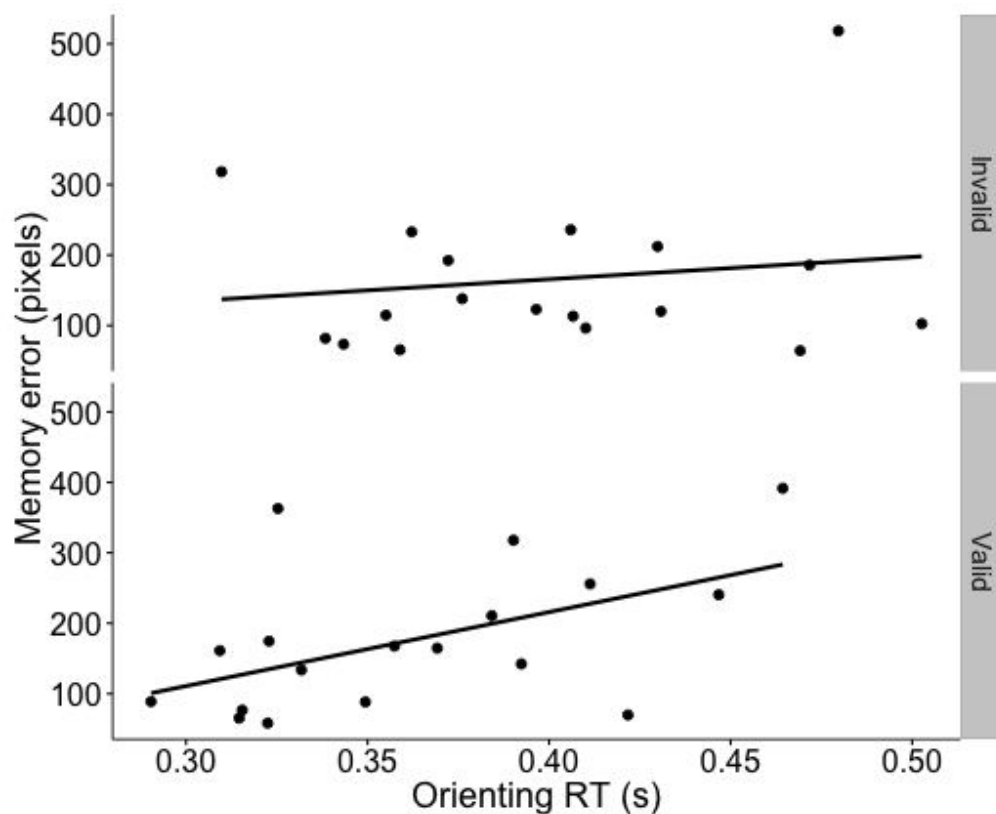


Figure 20. Depicts the significant relationship between memory error (pixels) during the memory phase and RT (s) during the orienting phase for subject averages for valid trials, but no significant relationship for invalid trials.

Follow-up analysis

Although results here are presented on models without including the length of the delay between timepoint one (the first visit) and timepoint two (the second visit) as a covariate, the following results also hold when including this covariate.

Memory phase (both timepoints)

AIC model averaging with memory error as the dependent measure and distractor, timepoint, and the distractor-by-timepoint interaction as fixed effects demonstrated coefficients for distractor and timepoint that were significantly greater than zero (Table 21). A repeated-measures ANOVA with two within subjects factors (distractor: social, non-social; timepoint: one, two) also revealed a main effect of timepoint, $F(1, 17) = 143.89$, $p < 0.001$, $\eta^2 = 0.89$, with poorer memory precision at timepoint two. However, there was no main effect of distractor, $F(1, 17) = 2.27$, $p = 0.15$, $\eta^2 = 0.12$. In light of the significant effect of distractor with model averaging, visual inspection shows poorer memory precision for social scenes compared to non-social scenes at both timepoints, however a greater difference at timepoint one (Figure 21).

Table 21
Memory error (pixels) during the memory phase, two timepoints

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	160.586	110.952	206.988	<0.001
Distractor	26.009	1.605	50.413	0.0367
Timepoint	210.351	172.096	248.808	<0.001
Distractor x Timepoint	-5.915	-48.82	36.989	0.787

For each parameter, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

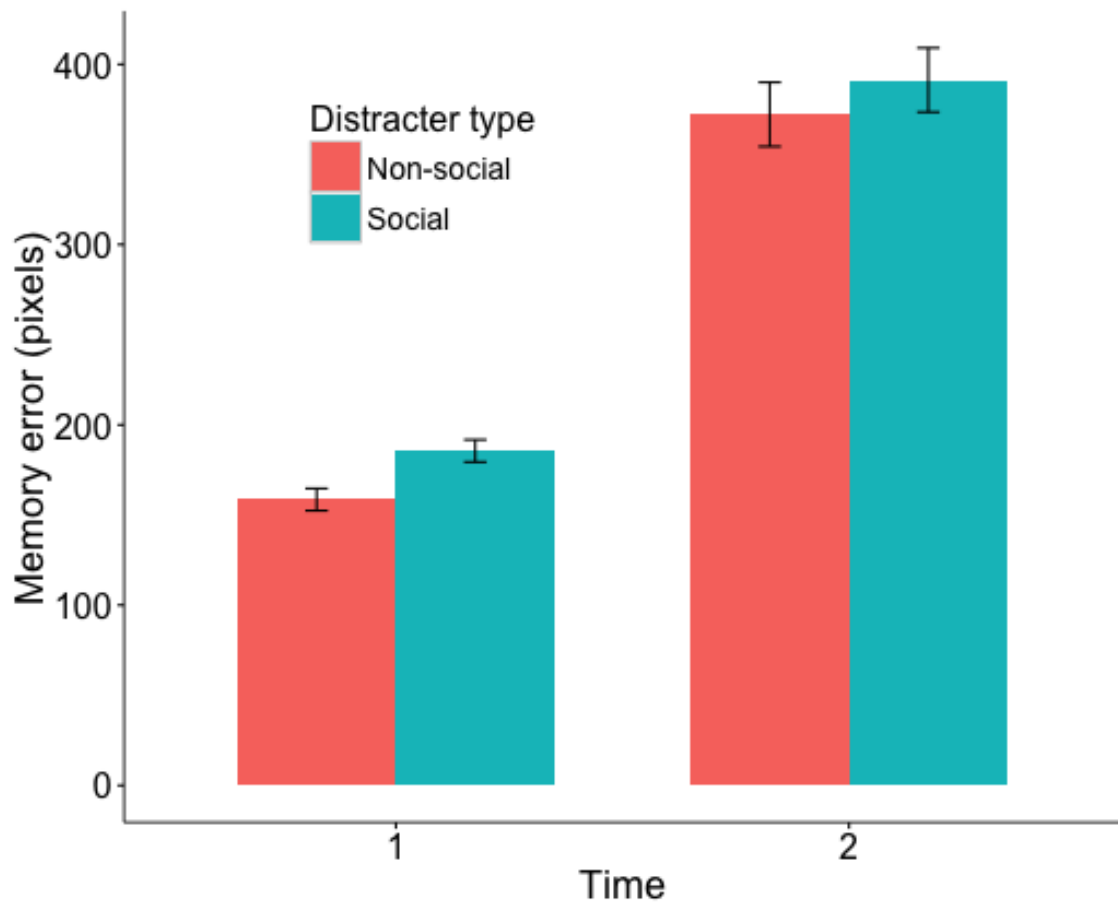


Figure 21. Mean memory error during the memory phase for timepoints one and two demonstrates poorer memory overall at timepoint two as well as a distractor effect of poorer memory for social compared to non-social scenes when investigating across both timepoints. Error bars are SEMs

In addition, because memory performance at timepoint two was particularly poor (close to 400 pixels away from the target on an image that is 1050 x 1680 pixels), we followed up to see if participants were performing above random levels. To do this, we took distances from the object location for a particular scene for a particular participant and a “recalled location” that was randomly chosen from that participant’s 80 recalled locations. We then computed participant averages for these random distances, and compared them to the social and non-social distances with paired-samples t-tests. Memory precision at timepoint two was significantly better than random for both social

and non-social scenes, $p < 0.001$ (random error: $M = 756.74$ pixels, $SD = 41.31$ pixels; social: $M = 388.47$ pixels, $SD = 137.72$ pixels; non-social: $M = 373.06$ pixels, $SD = 138.16$ pixels).

Finally, to address a potential concern that memory performance at timepoint two may have been affected by the validity of scenes during the orienting phase at timepoint one (such that invalid scenes may have introduced false memories), we analyzed timepoint two memory data including previous validity as a fixed effect in addition to distractor type. There were no significant effects of previous validity (results not shown).

Orienting phase (both timepoints)

Model averaging with accuracy (%) as the dependent measure and distractor, validity, timepoint, and all interactions between these variables as fixed effects was conducted. There was a significant effect of timepoint, with higher accuracy in timepoint one than two (timepoint one: $M = 98.38$, $SD = 0.03$; timepoint two: $M = 95.59$, $SD = 0.03$) (Table 22).

Table 22
Model averaging with parameters related to the dependent measures in the orienting, two timepoints

Predictor	RT (s)			p-value	Estimate	Accuracy (%)		
	Estimate	l-95% CI	u-95% CI			l-95% CI	u-95% CI	p-value
(Intercept)	0.396	0.372	0.419	<0.001	5.208	4.018	6.378	<0.001
Distractor	0.011	0.001	0.022	0.031	-0.24	-1.044	0.585	0.577
Timepoint	-0.009	-0.027	0.009	0.304	-2.025	-3.166	-0.852	<0.001
Validity	-0.033	-0.043	-0.021	<0.001	-0.011	-0.807	0.802	0.98
Distractor x Validity	-0.015	-0.028	-0.001	0.03	-0.077	-0.971	0.787	0.877
Timepoint x Validity	0.022	0.009	0.036	<0.001	0.644	-0.355	1.646	0.213
Distractor x Timepoint	-0.003	-0.019	0.012	0.688	0.65	-0.357	1.66	0.213
Distractor x Validity x Timepoint	0.015	-0.007	0.038	0.185	0.054	-1.987	2.095	0.959

For each parameter and dependent measure, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

AIC model averaging with the same fixed effects but RT (s) as the dependent measure showed the same significant effects as the orienting phase analysis described above (distractor, validity, and the distractor-by-validity interaction), as well as a significant validity-by-timepoint interaction term. A repeated-measures ANOVA with three within-subjects factors (distractor: social, non-social; validity: valid, invalid; timepoint: one, two) revealed a main effect of validity, $F(1, 17) = 57.18, p < 0.001, \eta^2 = 0.77$. There was also a significant validity-by-timepoint interaction, $F(1, 17) = 9.45, p = 0.007, \eta^2 = 0.36$, and a marginally significant distractor-by-validity interaction, $F(1, 17) = 3.74, p = 0.07, \eta^2 = 0.18$. Post-hoc analyses investigating the validity-by-timepoint interaction revealed that although the difference between valid and invalid trials was significant for both timepoint one ($p < 0.001$) and timepoint two ($p = 0.005$), there was a larger difference at time one (Figure 22). Although the distractor-by-validity interaction was only marginally significant, in light of the significant effect of this interaction term with model averaging, visual inspection shows a similar pattern of orienting effects at timepoint two as timepoint one, with longer RTs for social invalid compared to non-social invalid and little difference between social and non-social valid, although this difference is much less pronounced (Figure 22). Further, when averaging over timepoints one and two there was significantly longer RTs in social trials compared to non-social trials for invalid trials ($p = 0.029$), but no difference for valid trials ($p > 0.250$), similar to analyses for timepoint one only.

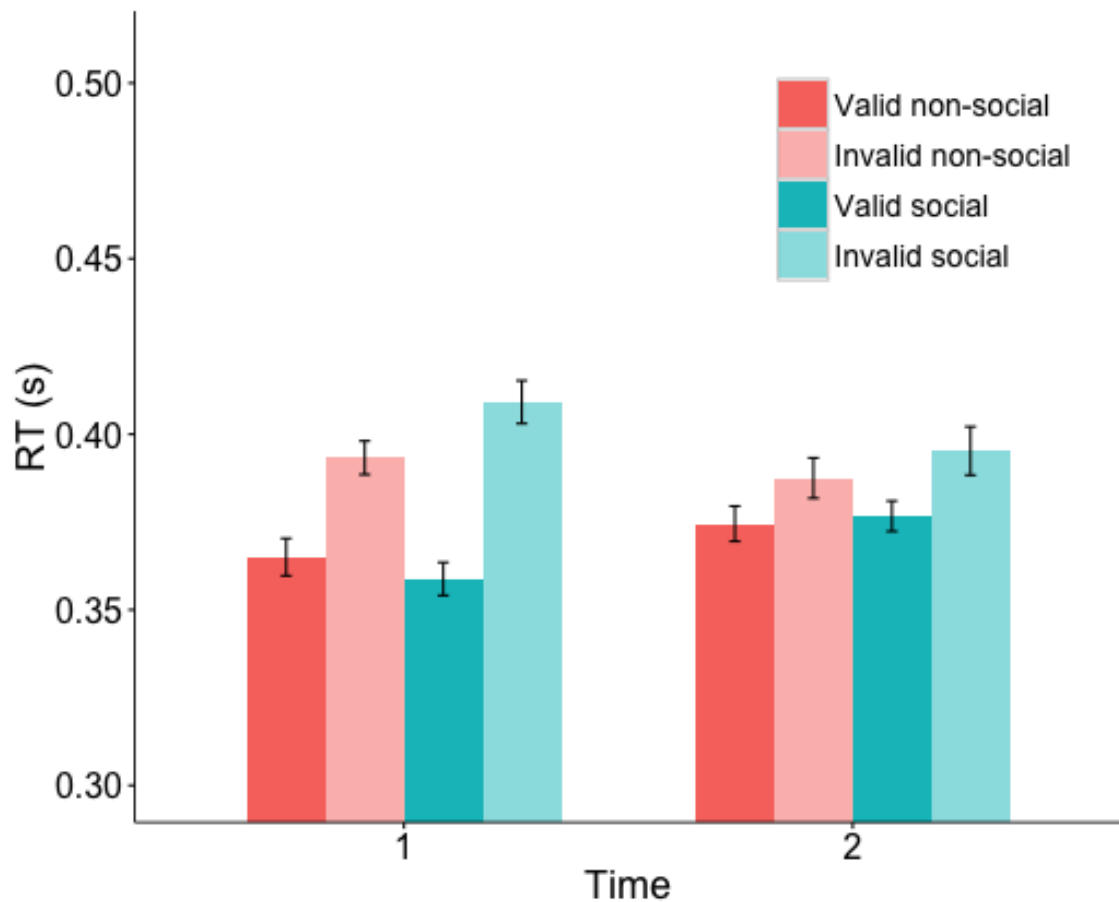


Figure 22. Mean RTs during the orienting phase at timepoints one and two demonstrate a greater validity effect overall at timepoint one compared to timepoint two, as well as a greater validity effect overall for social compared to non-social scenes driven by longer social invalid RTs. Error bars are SEMs.

EEG analyses

*Alpha desynchronization*⁵

EEG data were analyzed for the 3000-ms epoch during the orienting phase when the target was presented centrally, before the presentation of the scene cue.

⁵ This same analysis was run investigating alpha desynchronization contralateral compared to ipsilateral with respect to the *distractor* as opposed to the target. There were no significant differences detected for central targets associated with both social and non-social scenes, and therefore these results are not presented. Although it would be interesting to look at the interaction between distractor and target location, it was not possible to do so with the limited number of trials.

First, subject-level ERPs were analyzed, in order to investigate if the ICA was successful in removing ocular artifacts from the data. Plotting the topographies revealed activity indicative of ocular artifacts during the presentation of target objects associated with both social and non-social scenes (Figure 23). Despite multiple attempts to remove ocular artifacts completely with the ICA procedure, they proved difficult to remove. We therefore continued analyses, bearing in mind that ocular artifacts may drive spurious results. To determine if eye activity differed in response to target objects associated with social compared to non-social scenes, cluster-based permutation tests were conducted with subject-level ERPs including all channels over all timepoints, however no significant differences were detected.

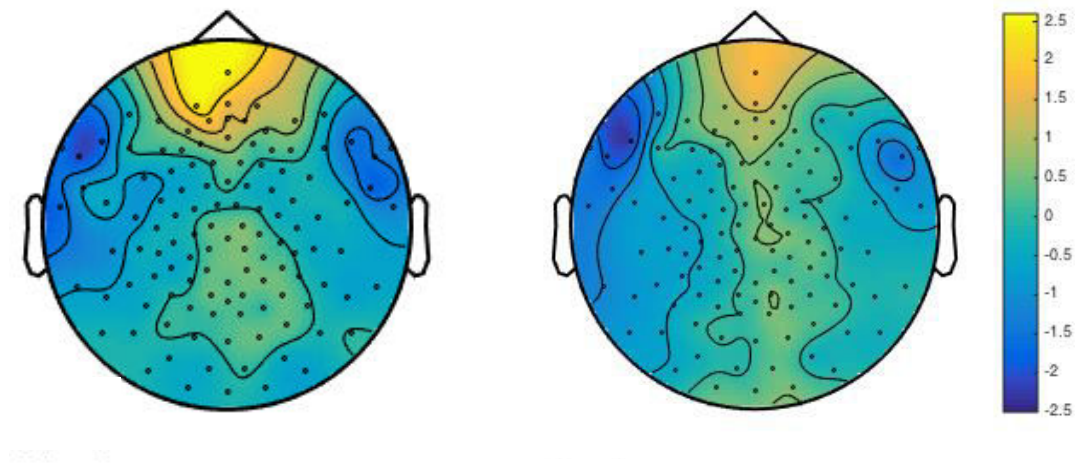


Figure 23. Average EEG activity over the 3000 ms post-stimulus of the centrally presented targets during the orienting phase for targets associated with social scenes (left) and non-social scenes (right). Values are μ Vs.

Cluster-based permutation tests using subject time-frequency averages in the alpha range (8-12 Hz) were used to determine if there was preparatory alpha desynchronization contralateral compared to ipsilateral to the location of the target

learned during visual search. There were no detectable significant differences between alpha power contralateral compared to ipsilateral for centrally presented targets associated with social scenes. There were, however, significant differences detected between 640-1120 ms ($p = 0.007$), and between 1640-3000 ms ($p < 0.001$) for targets associated with non-social scenes. Examining the topography of the difference between contralateral and ipsilateral alpha power during the second time period (1640-3000 ms) suggests this difference is strongest over posterior electrodes (Figure 24). Examining power for oscillations in the alpha range (8-12 Hz) over time for P7/8 electrodes (Stokes, Atherton, Patai, & Nobre, 2012a) suggests this difference to be due to alpha desynchronization contralateral compared to ipsilateral the target location (Figure 25).

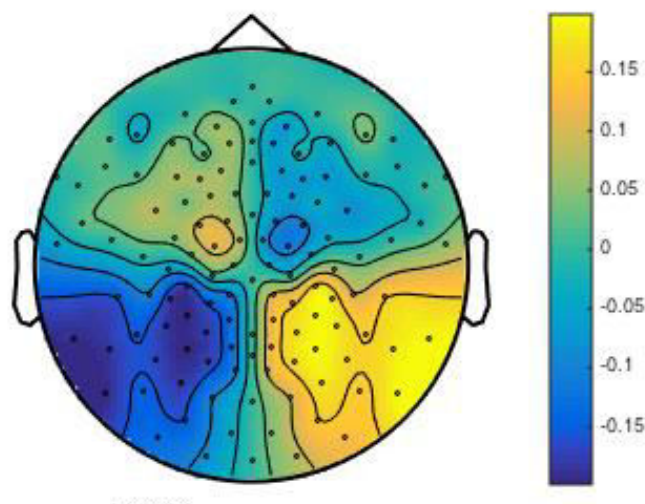


Figure 24. Average power in the alpha range (8-12 Hz) for the contralateral – ipsilateral difference in relation to learned target location in response to centrally presented targets associated with non-social scenes during the orienting phase. Trials with targets on the left hemifield are flipped such that all trials here appear as if targets are located in the right hemifield.

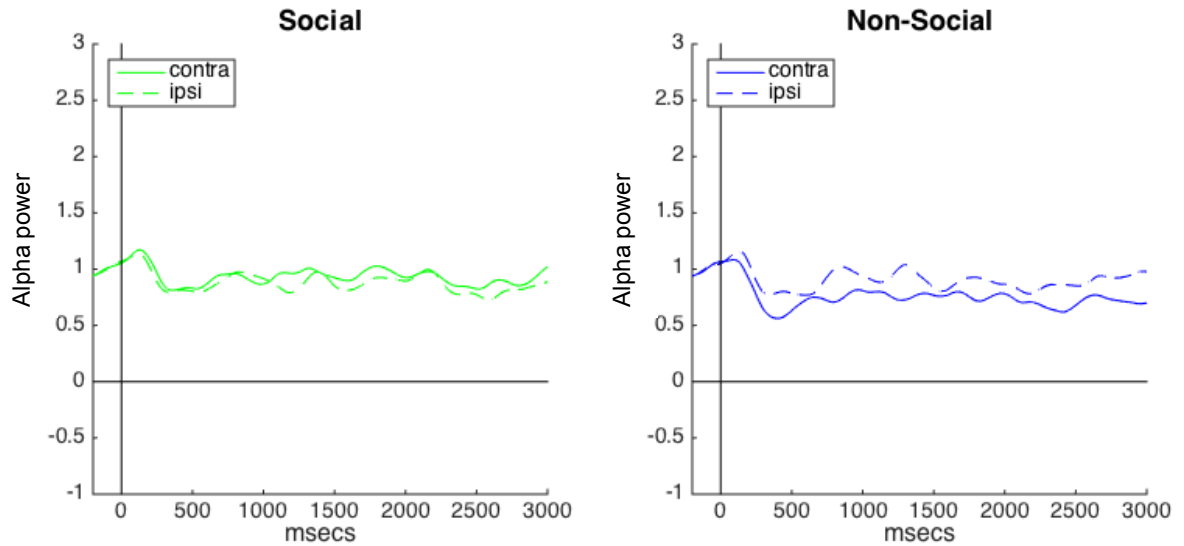


Figure 25. Average power in the alpha range (8-12 Hz) in P7/8 electrodes over time in response to centrally presented targets associated with social and non-social scenes during the orienting phase. Contra = contralateral to learned target location, ipsi = ipsilateral to learned target location. While alpha is significantly desynchronized contralateral compared to ipsilateral to target location in response to central targets associated with non-social scenes, there is no difference for social scenes.

In light of significant alpha desynchronization in response to centrally presented targets associated with non-social scenes, as well as the previous literature suggesting alpha desynchronization is associated with target locations held in memory (Stokes, Atherton, Patai, & Nobre, 2012a; Summerfield et al., 2011), we explored the relationship between alpha desynchronization and explicit memory for target locations. Participant averages for alpha power (8-12 Hz) in P7/8 electrodes over the two time segments that reached significance above (640-1120 ms and 1640-3000 ms) were each entered into two ANCOVAs (one for targets associated with social scenes and the other with non-social scenes), with one within-subjects factor (side: contralateral, ipsilateral) and memory error for that scene type as a covariate. For the first time segment (640-1120 ms), for non-social scenes, there was a main effect of side, $F(1, 16) = 13.83$, $p =$

0.002, $\eta^2 = 0.46$, with lower power contralateral compared to ipsilateral (see Figure 25). There was also a side by memory error interaction, $F(1, 16) = 5.42$, $p = 0.033$, $\eta^2 = 0.25$. Follow-up analyses revealed a significant negative correlation between ipsilateral – contralateral power and memory error, $r = -0.48$, $p = 0.044$, with greater desynchronization (higher ipsilateral – contralateral power) associated with lower memory error (pixel distance from recalled to actual target location). There were no significant effects for social scenes, or for social and non-social scenes during the second time segment (1640-3000ms).

N170

EEG data were analyzed for the first 500 ms after the presentation of the scene cue during the orienting phase, before the onset of the target within the scene. First, we investigated whether there were differences in brain activity between social and non-social scene cues, without comparing contralateral versus ipsilateral activity. Cluster-based permutation tests were conducted with subject-level ERPs including all channels over all timepoints. There was a positive difference (social - non-social) detected between 248 and 496 ms ($p = 0.002$), and a negative difference detected between 256 and 496 ms ($p = 0.015$). Exploring the topography for the difference between social and non-social scene cues (social - non-social) averaging over the two time periods (248-496 ms) reveals the positive difference to be located in posterior channels and right lateralized, while the negative difference appears to be fronto-central (Figure 26).

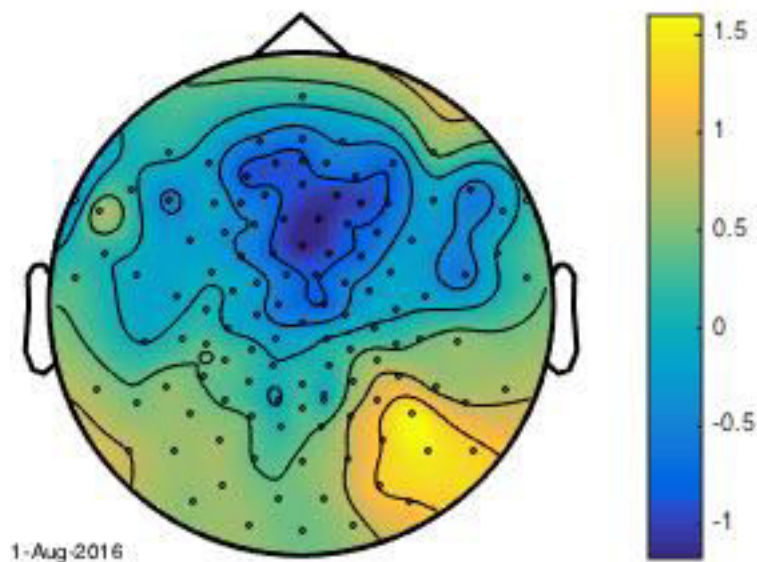


Figure 26. Average activity between 248-496 ms post-presentation of scene cue during the orienting phase for the social – non-social difference suggests the differences found in cluster-based permutation testing arise from a negative cluster in fronto-central electrodes and a positive cluster in right posterior electrodes. Values are μ Vs.

Plotting activity over time for the channel in each cluster where the difference appears greatest (P8 for positive cluster, channel 6 near to Fz for negative cluster) further elucidates this difference (Figure 27). To check whether ocular artifacts drove these differences, we investigated topographies for social and non-social scenes separately averaged over the timepoints (248-496 ms). These topographies did not show evidence of ocular artifacts during this time period (Figure 28).

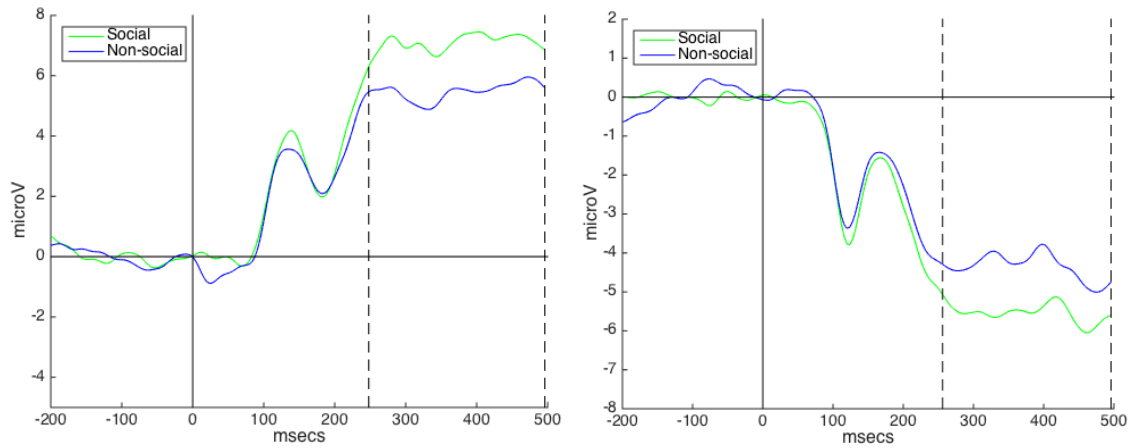


Figure 27. Average EEG activity over time for social and non-social scene cues in P8 (left) and electrode 6, close to Fz (right).

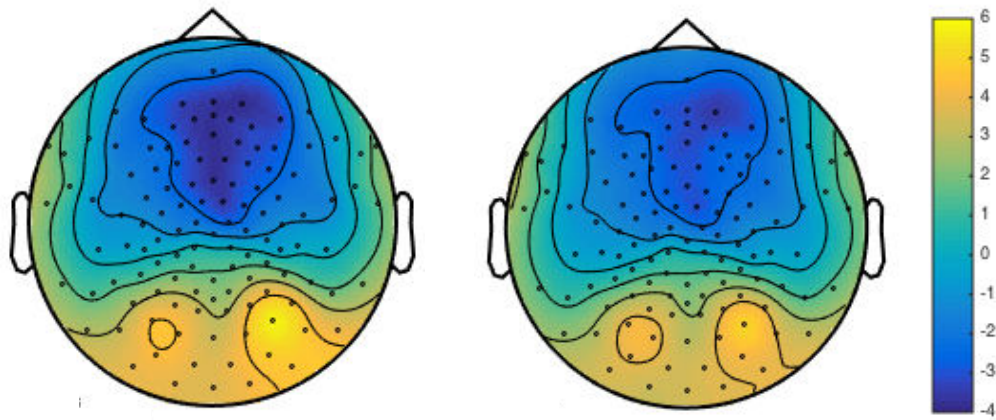


Figure 28. Average activity between 248-496 ms post-presentation of the scene cue for social (left) and non-social (right) scenes suggests no ocular artifacts. Values are μ Vs.

Next, to investigate whether the N170 occurs contralateral but not ipsilateral to faces embedded naturally within scenes, we analyzed the first 200 ms after the onset of the scene cue. Cluster-based permutation tests conducted with subject-level ERPs comparing homologous electrodes on either hemisphere over all timepoints revealed no detectable differences between contralateral and ipsilateral activity for social and non-

social scene cues separately. There were also no detectable differences in activity directly comparing social and non-social scene cues over all electrodes (comparing ipsilateral to ipsilateral and the same for contralateral, as opposed to comparing contralateral to ipsilateral).

Discussion

The current study sought to address three follow-up questions to Chapter 4. The first was whether the poorer explicit memory for social scenes seen in Chapter 4 would affect subsequent memory-guided attentional orienting in a Posner-style cueing task. While we replicated the previous result of poorer explicit memory for social scenes, and found that distractor type did moderate the validity effect during memory-guided attentional orienting, it was in the opposite direction than was expected. While we expected that poorer memory for social scenes might lead to a smaller validity effect, we showed a larger validity effect for social scenes, with a greater cost for invalid trials in particular. Interestingly, these explicit memory and orienting effects appear to persist after 1-3 weeks, and distractor type appears to moderate orienting effects even without the presence of the social and non-social distractors themselves. The effects at timepoint two are, however, much less pronounced and should be treated with caution. With regards to the second question—do we show a lateralized N170 potential similar to previous research (Towler & Eimer, 2015)—we did not find evidence of an N170, lateralized or otherwise, when viewing laterally-presented social stimuli embedded in natural scenes. However, we did find non-lateralized differences at later processing stages, 250 ms after stimulus onset, with a more negative potential in fronto-central electrodes and a more positive potential in right posterior electrodes for social compared to non-social scenes. Finally, as to whether we would see differential effects of

preparatory alpha desynchronization contralateral to the target location when participants viewed centrally presented targets, we did indeed find a difference. While there was significant desynchronization in the alpha range (8-12 Hz) contralateral relative to ipsilateral to target location when viewing targets associated with non-social scenes, there was no significant difference in alpha oscillations for targets associated with social scenes.

Important to note is the fact that the current study replicated the main results from the previous study in Chapter 4. First, we replicated here the difference in search time slopes between social and non-social scenes during the visual search task, with shallower slopes over three blocks for social scenes. This subtle difference was subsequently followed by a pronounced difference in memory precision, with poorer memory for social scenes, similar to the previous study. Finally, we replicated the cross-task relationship whereby search slope during visual search predicted memory precision in the memory phase, with shallow search slopes relating to poorer precision. With regards to first look, there was a subtle difference in the results between the two studies. Whereas participants in Chapter 4 made more first looks to social distractors compared to non-social distractors across blocks, participants in the current study only made more first looks to social distractors in the first block. Additionally, although we demonstrated a relationship between first looks and search time in Chapter 4, we did not observe the same relationship here. Given these discrepancies, it becomes clear that although participants may consistently demonstrate social distraction in their search times and memory precision, there is more variability in the degree of overt attention capture as measured by gaze behavior. Moreover, although we made the argument in the previous chapter that search time may be a mediating factor between gaze behavior and memory precision with regards to social distraction, in light of the current study it is more likely

that while overt attention capture may be a contributing factor to search time, it is neither necessary nor sufficient in demonstrating variation.

One intriguing finding from the current study is the fact that although we show *poorer* explicit memory for social compared to non-social scenes, we show a *greater* validity effect with a higher cost (slower RTs) for invalid social trials in particular. One explanation may lie in the cross-task analyses. We found that memory precision interacted with validity to predict RTs during the orienting phase, such that poorer memory precision related to longer RTs in valid trials, but there was no such relationship for invalid trials. As the distractor effect at the orienting phase was driven by *invalid* trials, this cross-task analysis suggests that something other than explicit memory may be driving differential orienting effects between social and non-social scenes. One hypothesis is that while explicit memory for social scenes is poorer, implicit memory, which has also been implicated in the orienting phase in addition to explicit memory (Summerfield et al., 2006), may be better. Indeed, other work with a similar paradigm and healthy ageing participants suggests that explicit contextual memory is not necessary for memory-guided attention to spatial locations in natural scenes (Salvato, Patai, & Nobre, 2016a; Salvato, Patai, McCloud, & Nobre, 2016b). Further research is necessary to explore this hypothesis. Another possibility is that the orienting phase was overall more difficult in trials with social scenes compared to non-social scenes. Previous literature reports larger validity effects with increased task difficulty for endogenous cues (arrow cues) compared to exogenous cues (Berger, Henik, & Rafal, 2005). Inclusion of neutral trials may help in exploring this hypothesis by determining if RTs are longer for neutral social compared to neutral non-social trials.

Interestingly, moderation of the orienting validity effect by distractor type, as well as the finding of poorer explicit memory for social scenes, are still present when

including data from following participants up approximately 1-3 weeks later. Caution is warranted, however, as these effects are much less pronounced at timepoint two and are dependent upon null interactions with timepoint that may need more power to detect. Additionally, these findings extend the literature on memory-guided attention orienting with natural scenes, which has previously demonstrated effects at the longest one day after the visual search task (e.g., Summerfield et al., 2006). We now know that participants can form robust long-term memories for relatively arbitrary spatial locations within natural scenes that persist even 1-3 weeks later, despite a relatively short learning experience (approximately 1 hour). Further, the current study suggests that subtle effects of attentional biases on memory, in this case social distraction, may be robust to time as well.

In addition, these follow-up results provide evidence against two possible hypotheses for the seemingly contrasting effects of distractor type between the memory phase and the orienting phase. One hypothesis is that while explicit memory may initially be poorer for social scenes, in the approximately 30 intervening minutes until the orienting phase memory degrades more rapidly for *non*-social scenes, such that by the time participants engage in the task their memory has become poorer for non-social scenes. However, the follow-up data provides evidence against this hypothesis, as poorer memory for social scenes appears to persist even 1-3 weeks later. Another hypothesis is that the distractor effect at the orienting phase is not due to distraction at encoding, but rather distraction during retrieval due to the presence of the social distractors within the scenes during the task. The follow-up data again provides evidence against this hypothesis. In the follow-up version of the orienting phase, the scenes and the distractors were not even present when participants reacted to the target's appearance, which occurred on a gray screen. The only cue they were given was the

centrally presented target, yet still there was a robust validity effect that appears to be moderated by distractor type.

However, caution is warranted when interpreting results including the follow-up data. Although we show a difference in memory performance that persists over several weeks, it is possible that reactivation of the memories during the first memory task led to further consolidation of this difference between social and non-social scenes. Perhaps if the only memory task were to have occurred three weeks later this difference would not be present. It is also possible that there was interference from the first orienting task on the second memory task; however, whether scenes were valid or invalid in the first orienting task did not relate to memory performance at timepoint two. With regards to the memory-guided orienting task, there are two important caveats to note. First, the time to follow-up was not the same length for every participant. Due to the fact that participants' initial visits occurred over the span of two weeks, time in between the two timepoints varied between participants. Although problematic, including the length of the delay for each participant as a covariate did not affect the results, and therefore we do not believe this limitation on its own invalidates our findings. In addition, although the order of scene presentation was randomized, the second memory-guided orienting task was identical to the first with regards to counterbalancing for each participant. Participants therefore saw the same scenes as valid and invalid (although during the follow up the scenes were not presented). It is possible this affected performance due to memory interference.

Perhaps the most interesting finding arises from investigating alpha desynchronization contralateral to learned target locations in response to centrally presented targets during the orienting phase. We detected significant desynchronization for targets associated with non-social scenes, but not for targets associated with social

scenes. Importantly, these targets were counterbalanced—while some participants saw a particular target and associated it with a social scenes, other participants associated that same target with a non-social scene. It is unlikely, therefore, that differences arose due to the perceptual properties of the stimuli. Moreover, the extent of alpha desynchronization related to explicit memory performance prior to the orienting task for non-social scenes, but not for social scenes. These findings suggest that the effect of social distraction on explicit contextual memory extends to neural activity, and specifically to lateralized alpha oscillations that have previously been shown to occur in response to perceptual cues (Romei et al., 2010; Worden et al., 2000), as well as memory cues (Stokes, Atherton, Patai, & Nobre, 2012a; Summerfield et al., 2011). Also, while the previous literature found alpha desynchronization in response to the scene cue with similar memory-guided orienting tasks using natural scenes (Stokes, Atherton, Patai, & Nobre, 2012a; Summerfield et al., 2011), the current study is the first instance of preparatory alpha desynchronization to centrally presented targets associated with a spatial location. However, caution is of course warranted due to the presence of ocular artifacts in the data.

It is interesting to note that we were not able to detect a N170 potential for our social stimuli, contralateral or otherwise, as has been detected previously for both central and lateral face presentation (Eimer, 2000b; Towler & Eimer, 2015). This is likely due to the small size of the faces and the complex nature of the stimuli. We did, however, detect more negative activity in fronto-central electrodes from approximately 250-500 ms post-stimulus for social compared to non-social scenes. This activity possibly resembles the N400 for faces: a negative potential peaking around 400 ms post-stimulus in centro-frontal electrodes thought to reflect the semantic processing of people (as it is elicited by names as well as face stimuli), which is larger for familiar compared

to unfamiliar faces (Bentin & Deouell, 2000; Eimer, 2000a; Schweinberger & Burton, 2003). In addition to possible N400 activity, we demonstrated more positive activity in posterior electrodes, particularly on the right, from approximately 250-500 ms post-stimulus for social compared to non-social scenes. This potential possibly resembles the P400, which is often described in the literature as the precursor to the N170 face potential seen in infancy (de Haan & Nelson, 1999; de Haan, Pascalis, & Johnson, 2002). Although it is mainly investigated in infancy, a similar potential, described as the P350, was seen in one of the original N170 papers for adults as well (T. Allison, Puce, Spencer, & McCarthy, 1999). Although this potential is often described bilaterally, in the current study we find it pronounced on the right side.

In summary, the current study extends the literature on memory-guided attention orienting, and in particular the literature utilizing memories of spatial locations within natural scenes, by demonstrating the moderating effect of attention biases using social distraction as a case study. Here, we show that an attention bias towards social stimuli, even when such stimuli are task irrelevant, affects explicit contextual memory, which subsequently affects memory-guided attention orienting. Moreover, there is preliminary evidence to suggest these effects are long lasting, present even several weeks after memory encoding. Finally, the effect of social distraction on memory can be seen at the neural level when investigating preparatory lateralized oscillations in the alpha range (8-12 Hz) in response to memory cues.

Similar to Chapter 4, these findings have implications for a wide range of attention biases described in the literature. In the context of this thesis, these findings have potential implications for autistic individuals. While Chapter 4 detailed how an atypical social attention bias could affect learning and memory, the current study demonstrated that this altered memory could in turn affect attentional orienting,

potentially reinforcing initial attention biases in a cascading manner. However, Chapters 4 and 5 have investigated adult participants. ASD is a neurodevelopmental disorder, and cascading effects are likely to be more critical earlier in development. Using a similar paradigm with younger children is therefore of theoretical importance, to this thesis and to the memory-guided attention literature in general. It is to this idea we now turn in the next chapter.

Chapter 6: The functional consequences of social attention/inattention: Development

Candidate contribution: The candidate significantly contributed to every stage of this study, including: experimental design and implementation, recruitment, data collection, analysis strategy, data analysis, and written report.

Introduction

While Chapter 5 extended the findings on the functional consequences of social distraction discussed in Chapter 4, by investigating the effect of social distraction on memory-guided attention orienting as well as exploring neural markers of these effects, an open question remains about these relationships during development. Do neurotypical children demonstrate memory-guided attention orienting to naturalistic social and non-social scenes in a similar manner to neurotypical adults? In particular, do children demonstrate a similar attention bias towards social stimuli compared to non-social stimuli that are equally salient with regards to low-level visual properties, as we have shown with adults? If so, does this bias have functional consequences on learning, memory, and later memory-guided attention orienting? Finally, are there relationships with autistic traits and social anxiety in neurotypical children?

With regards to memory-guided attention orienting, a small and growing literature suggests that children demonstrate contextual cuing effects similar to adults. Although a study using the original contextual cuing paradigm (Chun & Jiang, 1998) did not report a memory-guided attention effect with 10-year-old children (Vaidya, Huger, Howard, & Howard, 2007), another study using more child-friendly stimuli (cartoon red and blue fish) found contextual cueing in 5-10 year-old children (Dixon,

Zelazo, & De Rosa, 2010). The authors suggest these effects were the result of implicit learning, as the children were incapable of recognizing old displays in a subsequent recognition test. Further, there is evidence of a relatively stable contextual cueing effect across development, from 6 years to beyond 65-years-old (Merrill, Conners, Roskos, Klinger, & Klinger, 2013). However, it is useful to bear in mind that the mechanistic bases of contextual cueing demonstrated by children may not be identical to adults. In particular, studies suggest that distractor-target similarity hinders children more than adults (Y. Yang & Merrill, 2014), and that children are more sensitive to the ratio of attended to unattended distractors (Couperus, Hunt, Nelson, & Thomas, 2010) as well as to the signal-to-noise ratio present in the task (Y. Yang & Merrill, 2015b; 2015a). These differences indicate that potential immaturities in perceptual learning, selective attention, and/or working memory may affect performance in childhood.

In addition, while contextual-cueing tasks are thought to index the effects of implicit learning on memory-guided attention (although see Smyth & Shanks, 2008; Vadillo, Konstantinidis, & Shanks, 2016 for arguments against the implicit nature of learning in contextual cueing), no work to our knowledge has investigated the effects of children's explicit learning on memory-guided attention orienting. The current study therefore used the memory-guided attention orienting paradigm from the previous two chapters, in order to test this ability in children between 6 and 10 years of age.

With regards to whether children possess a similar attention bias towards social stimuli as adults, there is a vast literature describing the presence of a social bias in children. Seminal research with simple face-like stimuli suggests a preference towards faces in newborn babies (Morton & Johnson, 1991), highlighting a bias towards social stimuli present early in development (although see Cassia et al., 2004 for evidence for a non-face specific perceptual bias). Expanding on this research, other work suggests that

young infants attend preferentially to faces over other salient objects, even in complex scenes, although this bias develops between 3 and 9 months of age, with younger infants' fixations best predicted by low-level visual salience followed by a gradual development into focused attention to faces (Amso, Haas, & Markant, 2014; Frank, Vul, & Johnson, 2009; Kwon, Setoodehnia, Baek, Luck, & Oakes, 2016). Beyond attention to social stimuli over other stimuli in general, there is evidence that children process face stimuli similarly to adults (e.g., Mondloch, Pathman, Maurer, Le Grand, & de Schonen, 2007), and young children also demonstrate similar attentional biases to adults, specifically towards threatening faces (e.g., LoBue, 2009). It is therefore likely that children possess an attentional bias towards social stimuli that is similar to adults.

However, although children's social bias may be similar to adults, differences in general attention abilities may lead to differences in performance when compared to adults as in the current study. Following up on their study showing a development in attention to faces in natural scenes between 3 to 9 months, Frank and colleagues reported a relationship between attention abilities, as measured by visual search, and face preference in infants between 3-9 months (Frank, Amso, & Johnson, 2014). This study suggests that what drives increased attention to faces over infancy is not a change in the bias towards social stimuli itself, but rather an increased ability to inhibit competing salient stimuli and/or sustain attention to face stimuli. As the salient social and non-social stimuli in the current study are task-irrelevant, and serve as distractors during visual search, it is possible that children may show greater social-distraction effects in the current memory-guided attention orienting task due to immature attention skills, which lead to a reduced ability to inhibit social distractors.

Finally, as we investigated with adults in Chapter 4, it is possible that the degree of autistic traits as well as social anxiety within neurotypical children may play a

moderating role on the functional consequences of social distraction. It is often reported that children with ASD are less engaged by social stimuli (see Papagiannopoulou et al., 2014 for a meta-analysis). Given that memory-guided attention examined by contextual cuing appears to be intact in children with ASD (Barnes et al., 2008; J. Brown, Aczel, Jiménez, Kaufman, & Grant, 2010) and that ASD is associated with a reduced attention bias towards social stimuli (see Chapter 1), investigating autistic traits may be a way of quantifying an individual's degree of bias towards social stimuli that is not confounded with general task performance, as well as serve as a proxy for ASD symptoms (Senju & Johnson, 2009). In addition, similar to adults with social anxiety, children with generalized anxiety show an attentional bias towards both threatening and happy faces (Waters, Mogg, Bradley, & Pine, 2008). However, less research specifically investigates attentional biases towards emotional faces in *socially* anxious children. To investigate if social anxiety and autistic traits affects performance on our memory-guided attention-orienting task, similar to neurotypical adults in Chapter 4, we included scales to measure these individual differences in children.

To determine the presence of similarities or differences between adults and children when investigating the functional consequences of social distraction, we posed four complementary questions: 1) Will children demonstrate social distraction during visual search with natural scenes, similar to adult participants in the previous two chapters? 2) Will social distraction influence later memory performance, such that memory is poorer for social scenes, similar to adult participants? 3) Will the social nature of stimuli affect memory-guided orienting of attention, again similar to adult participants in the previous chapter? 3) Will these relationships be moderated by individual differences in social anxiety and autistic traits?

Methods and materials

Participants

The University of Oxford Central University Research Ethics Committee (CUREC) approved this research. Eighteen healthy child volunteers participated in this study. Two were excluded due to not completing the task, leaving 16 participants (aged 6-10, 9 female). In addition, sixteen healthy adult volunteers of the 18 from the previous study (aged 19-21, 14 female) were included in this study. Two participants from the previous study in Chapter 4 were excluded in order to have an equal number of participants per group, fully counterbalanced in terms of the characteristics of natural scenes to be learnt. Whereas previously it was important to have as large a sample size as possible for the EEG study, the priority for the current study was that the stimuli were counterbalanced in the same way for children and adults. All participants had normal or corrected-to-normal vision. All adult participants provided written informed consent and received course credit for their participation. For children, parents provided written informed consent and children provided verbal assent.

Procedure

Visual search

This procedure was the same as in Chapter 5 for both children and adults.

Memory phase

This procedure was the same as the previous chapter for both children and adults.

Orienting phase

This procedure was the same as the previous chapter for both children and adults, except for one difference. Whereas adults were capped in between the memory and orienting phases, as described in the previous chapter, children played in the waiting room for 30 minutes while parents filled out questionnaires. The task was the same for both adults and children, as described in the previous chapter. However, only eye tracking, and not EEG, was used with children, to assure participants maintained fixation. The experimenter also watched closely and reminded children to fixate centrally when necessary.

Questionnaires

Adult participants filled out the autism-spectrum quotient (AQ), adult version (Baron-Cohen et al., 2001)—a questionnaire designed to be sensitive to individual differences in the normal population—and the Liebowitz social anxiety scale (SAS) (Liebowitz, 1987). For child participants, parents filled in the child versions of these same questionnaires: AQ-Child (Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008) and Liebowitz SAS-CA (Masia-Warner et al., 2003).

Eye-tracking processing

Processing was performed in the same manner as the previous chapter for both children and adults.

Statistical analysis

Visual search

The measures used in the current study were the same as for the previous studies in Chapters 4 and 5: Accuracy was calculated as whether participants correctly clicked

on the target within a 0.63 degrees of visual angle buffer. Search time (time from scene onset to click on the target) and first look (whether the first saccade and associated fixation after scene onset was to the distractor), were both calculated only for trials in which the target was accurately located.

Memory phase

Memory error was measured as in the previous two chapters: distance in pixels from the accurate target location to the recalled location for trials in which participants accurately found the target object at least once during the visual search task.

Orienting phase

Dependent measures were calculated as in Chapters 4 and 5. Accuracy was calculated as trials in which participants correctly responded to the location of the target appearance (on the left or right hemisphere) with the left or right mouse button, within the reaction time window. Reaction time (RT) from target onset to mouse press was calculated for accurate trials. Included trials for reaction time analyses were also limited to trials in which participants accurately found the target object at least once during the visual search task, and trials in which the reaction time was within two standard deviations of the mean for that condition for that participant.

Individual differences

All analyses were rerun including the AQ and SAS as predictors, to determine the affects of autistic traits and social anxiety. However, these measures were missing for two children, therefore the sample size for these analyses was reduced to 16 adults and 14 children.

AIC modeling

For each dependent measure, model averaging was performed following the procedure outlined in Chapter 4. Random slopes were included in the mixed-effects models according to the “best-path” method described in the literature (Barr et al., 2013). All models were checked for the assumptions of normality and homogeneity of variance using visual inspection in *R*. If data were not normally distributed, data were transformed with natural log (ln). The variable manual search time was transformed due to positive skew. The covariates AQ and SAS were centered and normed to allow for appropriate interpretation of main effects in the presence of significant interactions in the AIC modeling approach. There was no significant correlation between the AQ and SAS, $r = 0.198$, $p > 0.250$.

Results

Visual search

Accuracy (%)

For this analysis, logit mixed-effects models (Generalized Linear Mixed Effects Models for binomially distributed outcomes) were used in AIC modeling. Model averaging revealed a significant effect of both age and block on the model (Table 23), with poorer accuracy for children ($M = 96.77\%$, $SD = 2.64\%$) compared to adults ($M = 98.27\%$, $SD = 2.09\%$). Overall, accuracy increased over blocks (block 1: $M = 96.63\%$, $SD = 2.83\%$; block 2: $M = 97.57\%$, $SD = 2.08\%$; block 3: $M = 98.36\%$, $SD = 1.91\%$).

Table 23
Model averaging with parameters related to the dependent measures during visual search

Predictor	Search time (ln(s))				First look (yes/no)				Accuracy (%)			
	Estimate	l-95% CI	u-95% CI	p-value	Estimate	l-95% CI	u-95% CI	p-value	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	1.188	1.08	1.295	<0.001	-1.953	-2.304	-1.61	<0.001	4.521	3.792	5.245	<0.001
Age	0.434	0.297	0.573	<0.001	0.273	-0.024	0.569	0.071	-0.882	-1.686	-0.079	0.032
Block	-0.556	-0.638	-0.468	<0.001	-0.108	-0.363	0.158	0.433	0.706	0.227	1.205	0.006
Distractor	-0.025	-0.062	0.011	0.175	0.615	0.229	0.996	0.002	0.129	-0.284	0.515	0.559
Age x Distractor	-0.011	-0.058	0.037	0.632	0.472	0.092	0.853	0.015	-0.329	-0.927	0.262	0.283
Block x Distractor	0.06	0.013	0.106	0.012	-0.484	-0.822	-0.146	0.005	0.024	-0.741	0.788	0.952
Age x Block	-0.116	-0.196	-0.036	0.004	0.226	-0.125	0.579	0.202	0.508	-0.24	1.25	0.185
Age x Block x Distractor	-0.061	-0.138	0.017	0.128	-0.319	-0.952	0.313	0.322	-1.067	-2.588	0.454	0.169

For each parameter and dependent measure, this table presents the averaged coefficient estimates (95%), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

Search time (s)

AIC model averaging with search time during the visual search task revealed that the coefficient estimates for both age and block were significantly different from zero, as well as the estimates for the block-by-distractor and age-by-block interactions (Table 23). A mixed-model ANOVA with two within-subjects factors (distractor: social, non-social; block: one, two, three) and one between-subjects factor (age: child, adult) revealed a main effect of age, $F(1, 30) = 22.01$, $p < 0.001$, $\eta^2 = 0.42$, with slower search times for children compared to adults. There was also a main effect of block, $F(1.93, 58.01) = 338.43$, $p < 0.001$, $\eta^2 = 0.92$, with search time decreasing over blocks. In addition, there was a marginally significant age-by-block interaction, $F(1.93, 58.01) = 2.65$, $p = 0.081$, $\eta^2 = 0.08$, and a marginally significant block-by-distractor interaction, $F(1.82, 54.58) = 2.99$, $p = 0.063$, $\eta^2 = 0.09$. The linear contrast of the block-by-distractor interaction reached significance, $F(1, 30) = 6.12$, $p = 0.019$, $\eta^2 = 0.17$. Extracting the regression slopes for each participant for social and non-social scenes separately showed steeper negative slopes for non-social scenes ($M = -0.31 \ln(s)$, $SD = 0.04 \ln(s)$) compared to social scenes ($M = -0.29 \ln(s)$, $SD = 0.04 \ln(s)$) (Figure 29). All other effects had $p > 0.250$.

Although the age-by-block interaction was only marginally significant in the ANOVA, due to the significant interaction with AIC modeling we followed this interaction further. Although there were very significant differences between blocks for children and adults separately (all $p < 0.001$), and likewise significant differences between adults and children for each block separately (block one: $p < 0.001$, block two: $p = 0.002$, block three: $p = 0.003$), inspecting Figure 29 shows a greater difference between children and adults in block one with this difference decreasing over blocks.

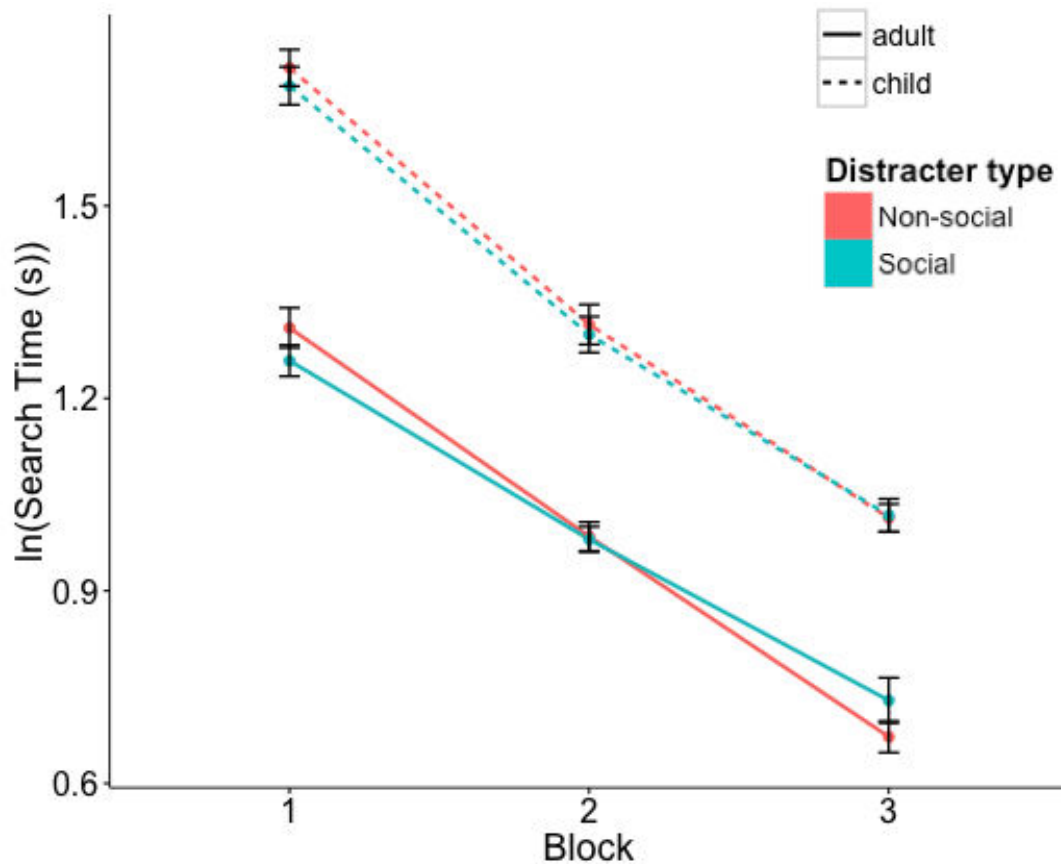


Figure 29. Log-transformed visual-search time over three blocks for children and adults. The distractor-by-block interaction had a significant effect on the model, with shallower search slopes for social scenes compared to non-social scenes for both children and adults, indicative of slower improvement over blocks for social scenes. Error bars are standard errors of the mean (SEMs).

First look (yes/no)

For this analysis, logit mixed-effects models (Generalized Linear Mixed Effects Models for binomially distributed outcomes) were used in AIC modeling. There were significant effects of distractor, as well as the age-by-distractor and distractor-by-block interactions on the model (Table 23). A mixed-model ANOVA with two within-subjects factors (distractor: social, non-social; block: one, two, three) and one between-subjects factor (age: child, adult) revealed a main effect of age, $F(1, 29) = 11.89$, $p = 0.002$, $\eta^2 =$

0.29, with a greater proportion of first looks to the distractor for children compared to adults. Main effects of distractor and block were also significant. The main effect of distractor, $F(1, 29) = 15.89$ $p < 0.001$, $\eta^2 = 0.35$, revealed more first looks to social compared to non-social distractors. The main effect of block, $F(1.89, 54.87) = 7.48$, $p = 0.002$, $\eta^2 = 0.21$, showed first looks decreasing over blocks. In addition, there was an age-by-distractor interaction, $F(1, 29) = 6.57$, $p = 0.016$, $\eta^2 = 0.18$, and a distractor-by-block-interaction, $F(1.98, 57.34) = 6.41$, $p = 0.032$, $\eta^2 = 0.18$. Post-hoc analyses revealed the distractor-by-block interaction to be driven by significantly greater proportion of first looks to social distractors compared to non-social distractors in block one ($p < 0.001$), but only a marginally significant difference in block two ($p = 0.087$) and no significant difference in block three ($p = 0.101$). Post-hoc analyses revealed the age-by-distractor interaction to be driven by significantly greater proportion of first looks to social compared to non-social distractors for children ($p < 0.001$), but not for adults ($p > 0.250$). This was due to a significantly greater proportion of first looks to social distractors for children compared to adults ($p > 0.001$), however no difference in proportion of looks to non-social distractors ($p = 0.207$) (Figure 30). All other effects had $p > 0.250$.

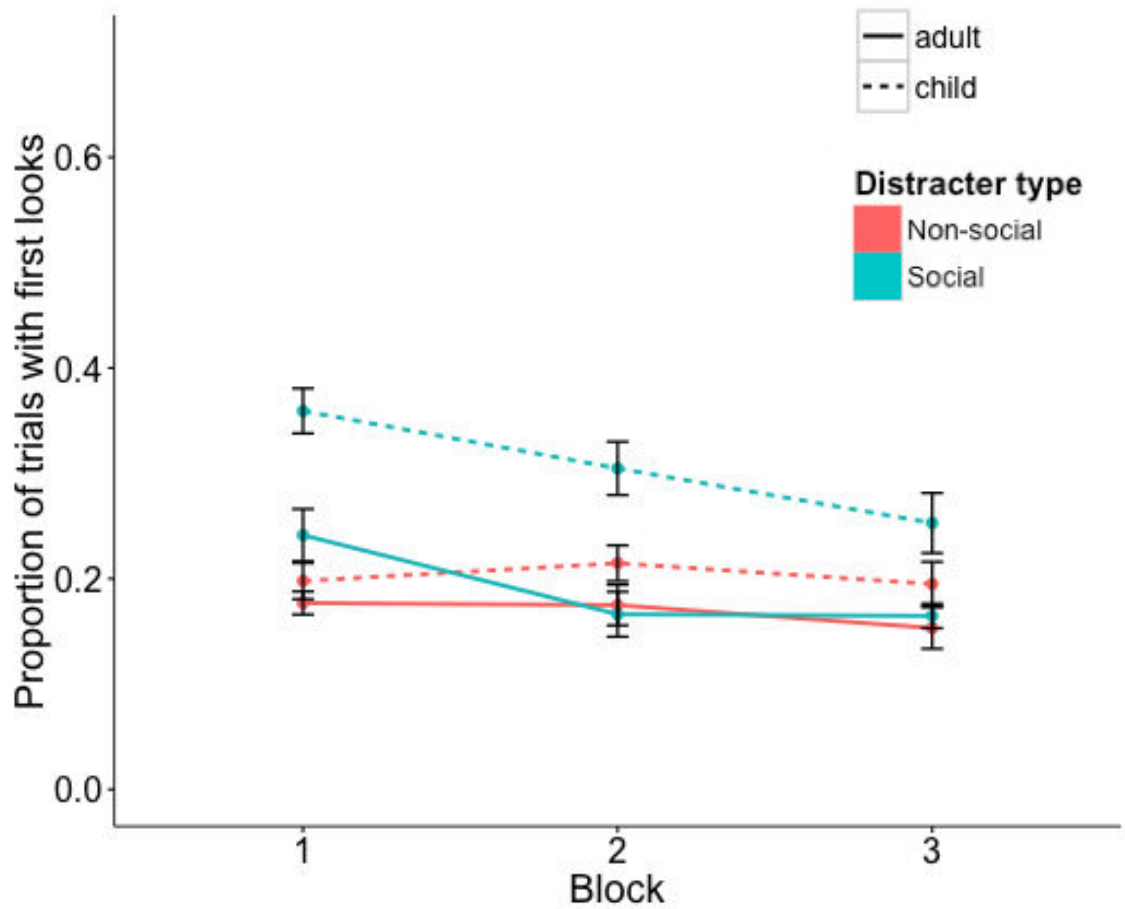


Figure 30. Proportion of trials with first looks to the distractor over three blocks for both children and adults. While children demonstrated a significantly greater proportion of first looks to social distractors compared to non-social distractors overall, adults showed only a significant difference in the first block, indicative of a rapidly diminishing attentional capture. Error bars are SEMs.

Memory phase

AIC model averaging revealed the coefficient estimates for age and distractor to be significantly different from zero (Table 24). A mixed-model ANOVA with one within-subjects factor (distractor: social, non-social) and one between-subjects factor (age: child, adult) showed a main effect of age, $F(1, 30) = 10.03$, $p = 0.004$, $\eta^2 = 0.25$, with better memory precision (smaller distance in pixels between recalled and actual

target location) for children compared to adults, and a main effect of distractor, $F(1, 30) = 14.28$, $p < 0.001$, $\eta^2 = 0.32$, with poorer precision for social compared to non-social scenes (Figure 31). The age-by-distractor interaction did not reach significance ($p = 0.110$).

Table 24

Model averaging with parameters related to memory error (pixels from target)

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	162.48	123.206	201.637	<0.001
Age	-85.14	-139.719	-29.91	0.002
Distractor	25.36	3.705	47.134	0.022
Age x Distractor	-18.78	-48.385	10.833	0.214

For each parameter, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

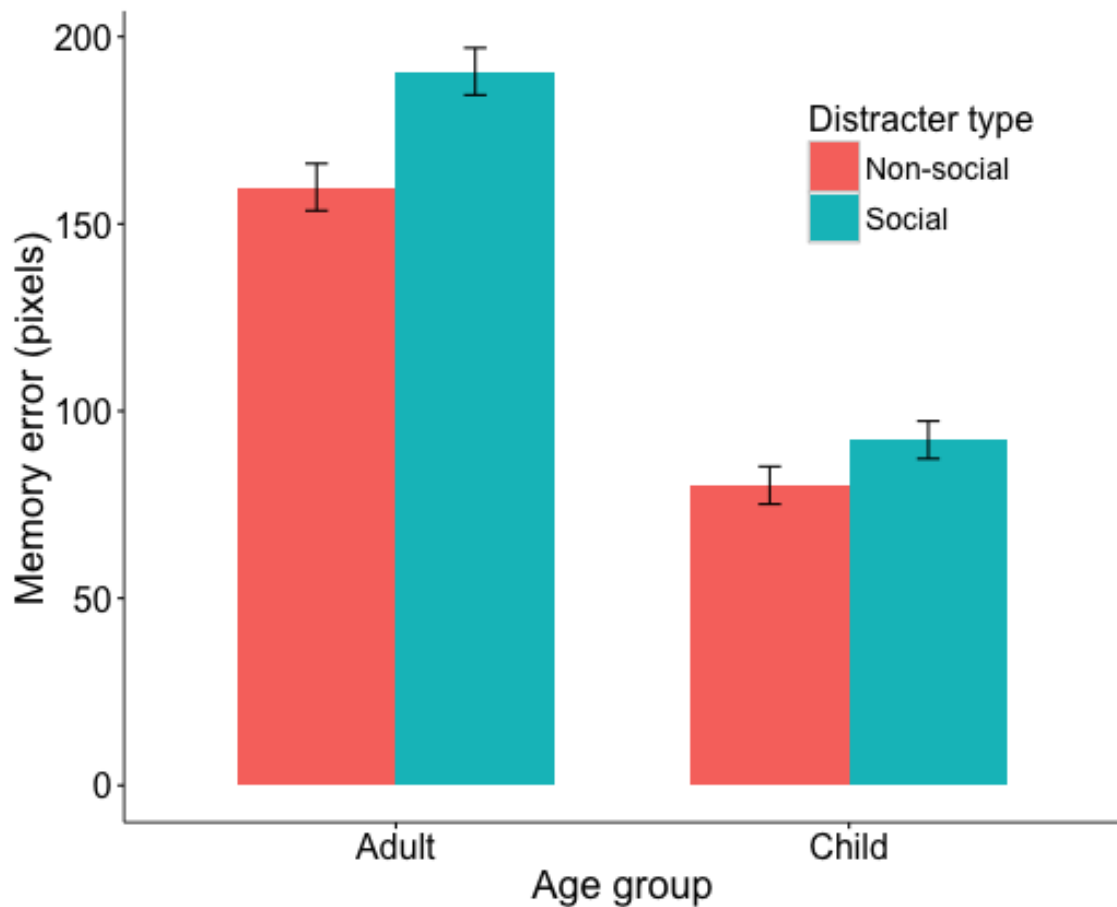


Figure 31. Memory error (distance in pixels between the recalled and accurate target location) for children and adults. Children demonstrated better memory precision compared to adults, while memory precision for social scenes was poorer compared to non-social scenes when including both children and adults. Error bars are SEMs.

Orienting phase

Accuracy (%)

For this analysis, logit mixed-effects models (Generalized Linear Mixed Effects Models for binomially distributed outcomes) were used in AIC modeling. Model analysis of accuracy in the orienting task revealed a significant effect of age on the model (Table 25), with poorer accuracy for children ($M = 88.62\%$, $SD = 9.83\%$) compared to adults ($M = 98.26\%$, $SD = 3.06\%$).

Table 25

Model averaging with parameters relevant for dependent measures during the orienting phase

Predictor	Estimate	RT (s)		p-value	Estimate	Accuracy (%)		p-value
		l-95% CI	u-95% CI			l-95% CI	u-95% CI	
(Intercept)	0.399	0.354	0.441	<0.001	4.89	3.914	5.83	<0.001
Age	0.175	0.116	0.24	0.001	-2.412	-3.492	-1.294	0.001
Distractor	0.011	-0.006	0.029	0.209	-0.264	-0.806	0.295	0.388
Validity	-0.035	-0.054	-0.013	0.002	-0.1	-0.805	0.667	0.804
Age x Validity	-0.037	-0.064	-0.009	0.009	0.549	-0.394	1.497	0.261
Distractor x Validity	-0.02	-0.042	0.002	0.073	-0.068	-0.736	0.609	0.86
Age x Distractor	-0.019	-0.042	0.003	0.097	0.231	-0.711	1.181	0.636
Age x Distractor x Validity	0.026	-0.004	0.056	0.087	0.225	-1.688	2.139	0.818

For each parameter and dependent measure, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

RT (s)

With RT during the orienting phase as the dependent measure, AIC model averaging revealed a significant effect of age, validity, and the age-by-validity interaction on the model (Table 25). There were also marginally significant effects of the distractor-by-validity, age-by-distractor, and the age-by-distractor-by-validity interactions. A mixed-model ANOVA with two within-subjects factors (distractor: social, non-social; validity: valid, invalid) and one between-subjects factor (age: adult, child) revealed significant main effects of age, $F(1, 30) = 29.13$, $p < 0.001$, $\eta^2 = 0.49$, and of validity, $F(1, 30) = 78.27$, $p < 0.001$, $\eta^2 = 0.72$. Children had slower RTs compared to adults, and RTs were slower overall for invalid compared to valid trials (Figure 32). There was also a significant interaction between age and validity, $F(1, 30) = 6.83$, $p = 0.014$, $\eta^2 = 0.19$. Post-hoc analyses following up the age-by-validity interaction revealed significant differences between children and adults for both valid and invalid trials ($p < 0.001$) as well as significant differences between valid and invalid trials for both children and adults ($p < 0.001$). However, examining the difference score

between invalid and valid trials showed a significantly greater validity effect for children compared to adults ($p = 0.015$) (Figure 32). There was no significant interaction between distractor and validity, $F(1, 30) = 2.30$, $p = 0.140$, $\eta^2 = 0.07$. All other effects had $p > 0.250$.

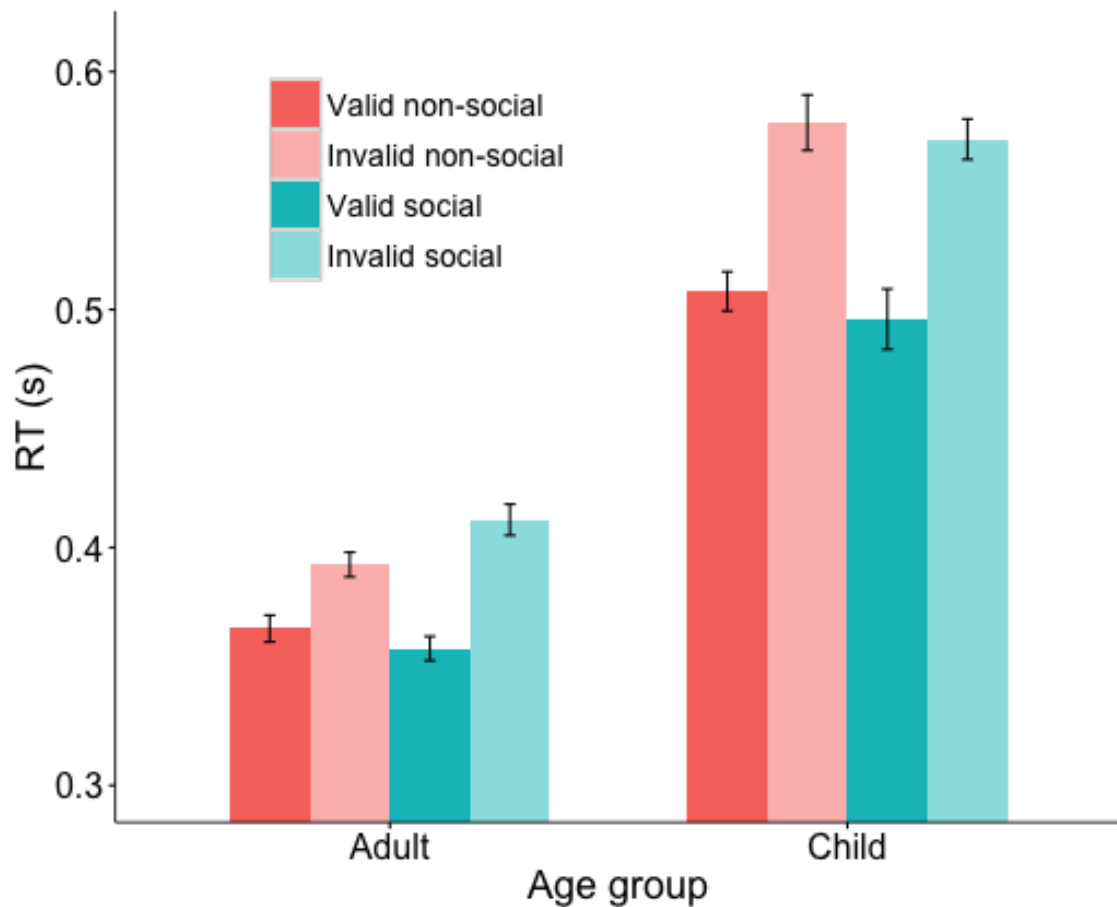


Figure 32. Reaction time (RT) in seconds during the orienting phase for both children and adults. Children were slower to react, but also demonstrated a larger validity effect (the difference between invalid and valid trials) when compared to adults. Error bars are SEMs.

Cross-measure relationships

Visual search, search time (s)

To investigate whether gaze behavior towards distractors predicted search time during the visual-search task, similar to adults in Chapter 4, and to test whether this relationship differed between children and adults, AIC model averaging was conducted with first look, distractor, age, and block as well as all possible interactions between these variables entered as predictors for search time. No significant effects or interactions occurred for first look (results not shown here).

Memory phase, memory error (pixels)

To investigate whether gaze behavior or search slope during the visual-search task predicted memory error during the memory phase, as well as whether this relationship differed between children and adults, search-time slope (the slope of the search times across all three blocks for a particular scene), first-look proportion (the proportion of the blocks out of three in which the participant made a first look at the distractor for a particular scene), distractor, age, and their interactions were entered as predictors for memory error in model averaging. In addition to the effects seen in the memory-phase analyses above (age, distractor), there was a significant effect of search-time slope, with shallower slopes associated with poorer memory precision, similar to the adults in Chapters 4 and 5. However, this effect was also qualified by a significant interaction between age and search-time slope (Table 26). Post-hoc analyses with subject averages revealed this interaction to be driven by a significant positive relationship between search-time slope and memory precision for adults ($r = 0.71$, $p = 0.002$), but not for children ($r = 0.14$, $p > 0.250$).

Table 26

Visual search measures (search-time slope and first-look proportion) as predictors for memory error during the memory phase

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	159.211	120.953	197.482	<0.001
Age	-81.99	-135.919	-28.178	0.003
Search-time slope	27.785	9.736	46.429	0.003
Distractor	26.691	4.794	48.465	0.017
Age x search-time slope	-25.894	-47.461	-4.358	0.019
Distractor x search-time slope	15.74	-4.988	36.437	0.138
First-look proportion	10.467	-6.147	26.779	0.216
Age x first-look proportion	-15.292	-36.421	5.929	0.159
Distractor x first-look proportion	-12.364	-33.323	8.667	0.251
Age x distractor	-3.815	-45.134	37.501	0.857
Age x search-time slope x distractor	-6.862	-48.38	34.151	0.745
Age x first-look proportion x distractor	15.005	-25.849	56.14	0.473

For each parameter and dependent measure, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

Orienting phase, RT (s)

Finally, to determine the presence of a relationship between memory precision during the memory phase and the validity effect in the orienting phase, as well as any differences in this relationship between children and adults, memory error, distractor, validity, age, and their interactions were entered as predictors for RT in the orienting phase. In addition to the effects seen in the orienting phase analysis above (age, validity, age-by-validity), AIC model averaging revealed significant interactions between memory error and validity, distractor and validity, and among age, distractor and validity (Table 27). Following up the interaction between memory error and validity showed there was a significant negative correlation between memory error and the validity effect (invalid – valid trials), $r = -0.38$, $p = 0.033$. Better memory precision (smaller error value) was associated with a larger validity effect. There were, however no significant correlations between memory error and RT for valid and invalid trials separately ($p > 0.250$).

Table 27

Memory error during the memory phase as a predictor for orienting phase RT

Predictor	Estimate	l-95% CI	u-95% CI	p-value
(Intercept)	0.4	0.352	0.446	< 0.001
Age	0.178	0.109	0.249	< 0.001
Memory error	-0.002	-0.011	0.006	0.557
Distractor	0.013	-0.005	0.032	0.179
Validity	-0.036	-0.06	-0.011	0.004
Age x distractor	-0.025	-0.054	0.003	0.095
Age x validity	-0.045	-0.081	-0.009	0.014
Memory error x validity	0.011	0.001	0.021	0.028
Distractor x validity	-0.025	-0.05	-0.001	0.047
Age x distractor x validity	0.042	0.008	0.076	0.015
Memory error x distractor	-0.004	-0.015	0.006	0.415
Age x memory error	-0.009	-0.036	0.018	0.51
Age x memory error x distractor	0.026	-0.007	0.059	0.122
Age x memory error x validity	0.013	-0.018	0.042	0.411
Memory error x distractor x validity	-0.003	-0.021	0.016	0.756
Age x memory error x distractor x validity	0.037	-0.029	0.103	0.268

For each parameter, this table presents the averaged coefficient estimates (θ s), and the 95% confidence intervals (CI, l = lower, u = upper) based on estimated unconditional variance. Estimates in bold differed statistically from zero based on 95% CIs with $p < 0.05$.

To follow up the age-by-distractor-by-validity interaction, model averaging was run for adults and children separately. Whereas adults demonstrated a significant effect of the distractor-by-validity interaction ($p < 0.001$), children did not ($p > 0.250$) (results not shown). Inspecting the data suggests this relationship is due to a larger validity effect for social scenes compared to non-social scenes for adults only, which was followed up in detail with these adults in Chapter 5 (Figure 32). Interestingly, while adults demonstrated the memory error-by-validity interaction ($p = 0.045$), children did not ($p = 0.190$) (results not shown).

Individual differences

First, t-tests were used to determine if AQ and SAS measures differed between children and adults, to test the assumptions of an ANCOVA. Although scores on the AQ did not differ between groups (adults: $M = 12.13$, $SD = 5.90$; children: $M = 14.86$, $SD =$

5.92), children had significantly lower scores on the SAS, $p < 0.001$ (adults: $M = 52.19$, $SD = 18.03$; children: $M = 24.79$, $SD = 16.93$)

All models were rerun including the AQ and SAS as predictors. Although the effects described above remained, there was no effect of or interaction with these measures that reached significance, therefore these analyses are not shown or discussed further.

Discussion

The current study sought to extend the research in both Chapters 4 and 5 by determining possible development in social distraction between children 6-10 years-old and young adults, as well as investigating any similarities or differences in the functional consequences of social distraction on memory and subsequent memory-guided attention orienting. Evidence suggested that children were indeed distracted by social stimuli, similar to adults in the previous two chapters. Although children were overall slower to locate targets in the visual search task, they demonstrated a similar difference in search slopes as discussed in the previous two chapters, with shallower search slopes for social scenes. In addition, eye-tracking revealed even greater attentional capture by social distractors for children, who showed a greater proportion of first looks to social distractors over all three blocks, whereas adults only demonstrated greater attentional capture to social distractors in the first block. Children's social distraction during visual search was followed by differential memory performance between social and non-social scenes. Intriguingly, children demonstrated better memory precision than young adults; however, both adults and children showed poorer memory precision for social scenes. Interestingly, poorer explicit memory for social scenes did not translate into differences in subsequent memory-guided attention

orienting for children, which differs from the adults described in the previous chapter. Children demonstrated a strong validity effect overall, but no difference in this effect between social and non-social scenes. Finally, there were no effects of individual differences for either social anxiety or autistic traits.

Apart from the social distraction effects, the current study extends the literature on memory-guided orienting in children. While it has been reported previously that school-age children are capable of more implicit memory-guided attention via the contextual cuing literature (Couperus et al., 2010; Dixon et al., 2010; Merrill et al., 2013; Y. Yang & Merrill, 2014; 2015a; 2015b), we report here for the first time that children are capable of memory-guided attention even when memories are acquired through an explicit learning task with naturalistic stimuli. Previous fMRI studies using the same memory-guided attentional orienting paradigm as the current study have implicated both the fronto-parietal orienting network, which has been described for perceptual-cue driven orienting as well as for memory-guided orienting, as well as a unique contribution of the hippocampus to memory-guided orienting exclusively (Stokes, Atherton, Patai, & Nobre, 2012a; Summerfield et al., 2006), although these associations have yet to be tested more causally with lesion patients. The current study therefore supports the idea that although the medial temporal lobe, including the hippocampus, continue to develop into adolescence, (Ghetti & Bunge, 2012; Menon, Boyett-Anderson, & Reiss, 2005; Paz-Alonso, Ghetti, Donohue, Goodman, & Bunge, 2008), some functional aspects of this brain system may be early developing.

An open question from this research stems from the finding of greater attentional capture by social stimuli for children compared to adults. The fact that there was no difference in attentional capture to equally salient non-social distractors between children and adults suggests that children did not show an overall bias towards

perceptually salient stimuli, but rather the effect was specific to social stimuli. This finding is consistent with literature demonstrating a bias towards social stimuli in young children that goes beyond low-level perceptual salience (Amso et al., 2014; Frank et al., 2009; Kwon et al., 2016). It also extends the literature that suggests a similar bias towards and processing of faces between children and adults (LoBue, 2009; Mondloch et al., 2007), to suggest an even stronger attentional capture by social stimuli in children. Whether this was due to a greater social bias or rather due to more general attention immaturity, such as a poorer ability to inhibit attention capture by the irrelevant social stimuli, could not be determined by the current study. Further work is necessary to explore the mechanism behind greater attentional capture by social stimuli in children.

Perhaps one puzzling aspect of the current study is the overall enhanced memory precision for children compared to adults in the explicit memory task. Previous studies have shown protracted development of memory precision between 6-10 years for working memory (Burnett Heyes, Zokaei, & Husain, 2016), episodic memory (e.g., DeMaster & Ghetti, 2013), as well as, most germane to the current discussion, spatial relational place learning (E. L. Townsend, Richmond, Vogel-Farley, & Thomas, 2010). One possibility is that children may have been more motivated to complete the task well. Although adults and children participated in the same task, including the “Despicable Me” themed features, anecdotally children were much more engaged with earning points. Another possibility is that the significantly longer search times for children during the visual-search task proved beneficial for memory performance. Longer search times compared to adults may have allowed children to encode the context of the scenes better, enhancing memory precision for target locations. Indeed, a study with children 8-12 years old found a u-shaped relationship between search speed

and contextual cueing effects, with intermediate length search speed associated with the largest contextual cueing effect (Darby, Burling, & Yoshida, 2014). Furthermore, other work suggests that attentional guidance only improves contextual cueing in adults when participants are forced to take longer to find targets due to increased difficulty (Kunar, Flusberg, & Wolfe, 2008).

Interestingly, although adults showed a relationship between search slope in the visual-search task and memory precision in the memory phase followed by a relationship between memory precision and RT in the memory-guided orienting phase, these cross-task relationships do not exist for children when analyzing them separately. At first glance, this difference suggests that only in adults does social distraction act mechanistically to affect explicit memory, which in turn affects subsequent attention orienting. However, it is possible this discrepancy is due to the overall better memory precision for children discussed above, as well as the overall slower RT in the orienting phase—general performance differences that may overpower any relationships across the tasks. Moreover, it may be that for children what is more relevant to memory performance is not the learning slope over blocks, as we explored here, but simply length of search time overall regardless of improvements over blocks, or the regression intercept. It is perhaps overall slower search times, either calculated by the average of the three blocks or the intercept, that may lead to better memory performance for children (as discussed above), whereas in adults the slope may be more important. It is also possible that the mechanism underlying these tasks is different for children. While memory-guided orienting in the current study may be driven by more explicit memory for adults, it is possible that implicit memory is more important for children. Further study is necessary to investigate these hypotheses.

In addition, gaze behavior during the search task did not relate to search time for both children and adults, similar to Chapter 5 but dissimilar to Chapter 4. This finding further highlights the idea discussed in Chapter 5 that, although attention capture by distractors may affect search time in some instances, it is not the greatest influence. Clearly, the presence of the social stimulus, whether or not it is the first item fixated, is distracting in its own right. Gaze behavior and search time also diverged with regards to social distraction—while search time indicated social distraction over all three blocks, first look suggested social distraction only in the first block. It is therefore possible that these measures reflect different aspects of social distraction: while first looks may index more automatic distraction effects, search time may index more voluntary task relevant processes. This hypothesis could be investigated in further study.

One limitation of this study was the use of images of adults as stimuli, which may not have been the best for eliciting social distraction in children. This is particularly relevant in light of the literature that demonstrates an “own-age bias” for face recognition, such that memory for faces is poorer for faces that are of a different age group than yourself (see Rhodes & Anastasi, 2012 for a meta-analysis). This may account for the fact that although there was poorer memory for social scenes when including both children and adults, this difference was not as pronounced for children.

Another limitation is the relatively small sample size with which to detect individual differences. Although there were no effects of or interactions with the SAS and the AQ within our analyses, caution should be used when interpreting the null effects for several reasons. First, the current study had an overall smaller sample size: $n = 30$ compared to $n = 37$ in Chapter 4. In addition, although covariates were standardized (centered and normed) to the full sample including children and adults, there were differences between children and adults in SAS scores in particular, with

lower SAS scores for children. Ideally children and adults would be normed for their age, which may eliminate differences between groups, however this procedure is not available for these measures. In addition, while measures were self-report in adults, the same measures were parent-report with children, which could account for differences between groups. Future research could look at individual differences in children specifically, with a larger sample size to detect such differences.

In conclusion, the current study extends the literature on memory-guided attention in children by demonstrating the capacity for more explicitly acquired memories to affect attention orienting in 6-10 year-old children. The current study also demonstrates the ability of social stimuli to distract children during visual search, however this social distraction has more subtle subsequent effects on memory, and potentially no effect on memory-guided attention orienting, in contrast to young adult participants. Importantly for this thesis, the current study shows the feasibility of this paradigm for school-age children, which allows for future study with children diagnosed with ASD. The current thesis hypothesizes that atypical social attention in ASD may be associated with impaired social functioning though the functional consequences of attention biases on memory and subsequent memory-guided attention in a cascading manner. Thus, it is crucial to investigate as early in development as possible, to capture when such a cascade may have the most impact.

Chapter 7: General discussion

As discussed in the introduction, atypical attention can be seen in both experimental and anecdotal reports of autism spectrum disorder (ASD). Although many aspects of attention have been investigated, including the often quoted triad of arousal, orienting, and executive control systems (see Keehn et al., 2013 for a review), the current thesis focused on selective attention in particular. This focus was due to the wealth of previous studies investigating selective attention in particular, as well as a desire to study a subset of attention with potentially high developmental impact in ASD, which previous researchers have suggested may be the case for selective attention (see Chapter 1). Furthermore, this thesis investigated both non-social and social specific selective attention in the context of ASD.

One account of atypical selective attention in ASD suggests that early domain-general alterations may have cascading effects over developmental time that lead to altered social cognition and the social impairments that are the hallmark of ASD. In order to test this account, we investigated two complementary questions. First, does early atypical non-social attention predict later social impairments in the context of ASD? Second, does a reduced social attention bias (which some researchers argue is the result of atypical non-social selective attention: Mundy et al., 2009; Senju & Johnson, 2009) act mechanistically to increase social impairment in ASD through learning and memory, such that autistic individuals learn and remember less about people and the social world? To ask these questions, the current thesis incorporated two experimental methods utilizing differing timescales.

Synopsis of findings

The first method addressed the potential causal relationship of atypical non-social selective attention on social functioning in ASD, by investigating relationships between attention and social impairment over longitudinal time. In Chapter 2 this method was applied with a sample of young children at familial risk for ASD (by having an older diagnosed sibling) and focused on the cognitive level. In Chapter 3 we investigated children with fragile X syndrome (FXS), a disorder well known for its high risk for behaviorally defined disorders such as ASD and attention-deficit/hyperactivity disorder (ADHD), and focused on the symptoms level of atypical attention and social functioning.

Chapter 2 utilized a multi-target visual search cancellation task with naturalistic objects as targets and distractors in a sample of 3-year-old children at familial risk for ASD. This study allowed us to ask novel questions about visual search in this group, as well as investigate longitudinal relationships between attention and social cognition measures. We hypothesized that poor performance in categorical search, where targets represent a category (animals), and enhanced performance in perceptual search, where targets are perceptually similar to distractors, would relate to high ASD symptom severity. Additionally, we hypothesized that co-occurring ADHD symptoms might relate to poor search organization and systematicity. Finally, we argued that a unidirectional relationship, whereby early attention predicts later social cognition but early social cognition does not predict later attention, would be indicative of a role of atypical attention in social functioning.

Our study suggested that the search superiority thus far associated with ASD symptoms may only be evident under restricted experimental conditions, including single target search with targets/distractors distinguished by few visual features. In our multi-target cancellation task with more complex stimuli, ASD symptoms were

associated with more disorganized search across conditions, and poorer search efficiency for categorical search in particular, consistent with reported poor conceptual knowledge in ASD (Naigles et al., 2013). In addition, ADHD symptoms contributed to search disorganization independently of ASD symptoms, comparable to previous reports of disorganized large-scale search in ADHD (Rosetti et al., 2016). Finally, we indeed found a unidirectional relationship: enhanced 2-year-old single-target visual search predicted poor face recognition at 3-years, but 2-year-old face popout did not predict 3-year-old search cancellation. This relationship indicates that perhaps atypical non-social attention in infancy plays a causal role in the social impairments seen in ASD, although this approach also highlighted a number of caveats, and directions for future research necessary to make stronger claims, to which we return later.

Chapter 3 took a similar longitudinal approach as Chapter 2, but with a population at high risk for *both* ASD and ADHD (boys with fragile X syndrome) instead of a population primarily recruited for high risk for ASD alone. In addition, instead of looking at atypical attention and social impairment at the cognitive level, in this chapter we investigated the symptoms level, with high ADHD symptoms indicative of atypical attention (although see the discussion in Chapter 3 on caveats to this statement) and high ASD symptoms indicative of social impairment.

Again, we found a unidirectional relationship such that early ADHD symptoms predicted later ASD symptoms, but early ASD symptoms did not predict later ADHD symptoms. Importantly, this relationship held when including severity of impairment as measured by IQ. This finding converges with previous literature in neurotypical individuals, which suggests a stronger predictive relationship of ADHD symptoms on ASD symptoms over development as opposed to the reverse (St Pourcain et al., 2011; Taylor et al., 2013). Chapter 3 was therefore consistent with the findings in Chapter 2,

while investigating another population of children at the symptoms level as opposed to the cognitive level. Again, future directions integrating the cognitive and symptom level approach will be discussed later.

The second method of study in this thesis looked more mechanistically at the potential role of atypical selective attention on a smaller timescale, and did so with older individuals. How might atypical social attention, like that seen in ASD, affect learning and memory on the scale of hours to weeks? Chapters 4-6 addressed this question in neurotypical individuals, as well as investigated neural underpinnings and developmental differences, with implications for autistic individuals and hope for future study.

Chapter 4 introduced the paradigm to be used for Chapters 4-6, which was developed to investigate the functional consequences of social distraction on attention, memory, and memory-guided attentional orienting. First, using a visual search task with natural scenes, we replicated the strong effects of social distraction on attention, but critically, even when compared to distraction from items with similar low-level visual salience, as indexed by a computational algorithm. Eye-tracking showed greater attentional capture by social stimuli during search, and search time also indicated that learning over blocks was moderated by distractor type, with a shallower learning slope for social scenes, consistent with social distraction in neurotypical individuals during simple (less naturalistic) visual search (Langton et al., 2008; Riby et al., 2012). Second, we showed for the first time that the effects of social distraction were not isolated to visual search, but extended to subsequent memory for target locations, with poorer memory precision for social scenes. Finally, social anxiety modulated memory precision, with better memory performance under social distraction for high-anxiety participants, perhaps in accordance with a hypervigilance-avoidance account

(Vassilopoulos, 2005). In contrast, autistic symptoms did not moderate performance, but rather individuals with higher autistic symptoms demonstrated generally reduced attentional capture for both social and non-social distractors.

This work suggests that encounters with distracting social stimuli affect not just the here and now, but subsequent memories built from perceptual/learning interactions. More importantly, this effect is modulated by individual differences in sensitivity to social stimuli. Attentional biases, such as a social attention bias, therefore not only operate in a selective attention domain, but also have functional consequences on memory.

Chapter 5 then sought to address several follow-up questions to Chapter 4. The first was whether the poorer explicit memory for social scenes would affect subsequent memory-guided attentional orienting in a Posner-style cueing task. While we replicated the previous result of poorer explicit memory for social scenes, and found that distractor type did moderate the validity effect during memory-guided attentional orienting, it was in the opposite direction than was expected. While we expected that poorer memory for social scenes might lead to a smaller validity effect, we showed a larger validity effect for social scenes. Interestingly, these explicit memory and orienting effects appear to persist after 1-3 weeks, and distractor type appears to moderate orienting effects even without the presence of the social and non-social distractors themselves, although caution is warranted due to these interpretations being based in part on null results.

Secondly, we investigated the neural correlates of social distraction's effect on memory. We found differences in preparatory alpha desynchronization contralateral to the target location stored in memory when participants viewed centrally presented targets, desynchronization previously seen in response to mnemonic cues for memory-guided orienting in natural scenes (Stokes, Atherton, Patai, & Nobre, 2012a;

Summerfield et al., 2011). While there was significant desynchronization in the alpha range (8-12 Hz) contralateral relative to ipsilateral to target location when viewing targets that had earlier been associated with non-social scenes, there was no significant hemispheric difference in alpha oscillations for targets associated with social scenes. Correlations with explicit memory performance for non-social scenes suggest the greater desynchronization when viewing non-social associated targets was associated with higher memory precision.

Attentional biases therefore operate not only in the selective attention and memory domains: the functional consequences of attentional biases on memory affect memory-guided attention orienting, which may in turn reinforce these biases. This idea has implications for ASD, as this study suggests a possible mechanism in which inattention to social stimuli may result in poorer memory for social information, which may lead to increased inattention to social stimuli, and so on, in a cascading manner.

Finally, Chapter 6 sought to extend the research in both Chapters 4 and 5 by determining possible age-related differences in social distraction between children 6-10-years-old and young adults, as well as investigating any similarities or differences in the functional consequences of social distraction on memory and subsequent memory-guided attention orienting. Children were indeed distracted by social stimuli, similar to adults in Chapters 4 and 5, as evidenced by eye-tracking and search times. In addition, eye-tracking revealed even greater attentional capture by social distractors for children. Children's social distraction during visual search was followed by differential memory performance for social and non-social scenes when including both children and adults. Intriguingly, children demonstrated better overall memory precision than young adults. Interestingly, poorer explicit memory for social scenes did not translate into differences in subsequent memory-guided attention orienting for children, which differs from the

findings for adults described in Chapter 5. This work extends the contextual cuing literature in school-aged children (Dixon et al., 2010; Vaidya et al., 2007; Y. Yang & Merrill, 2015a) to demonstrate more explicit memory-guided orienting as well.

Implications for theory and limitations

These experimental findings and the conclusions we have drawn from them have relevance to the everyday lives of individuals with ASD. As a National Autistic Society poster reads: “When a person with autism walks into a room the first thing they see is: A pillow with a coffee stain shaped like Africa, a train ticket sticking out of a magazine, 25 floorboards, a remote control... So it’s not surprising they ignore you completely.” We believe it illustrates nicely how non-social processing characteristics in general, and atypical attention in particular, can lead to the prominent social impairments that manifest in daily life for autistic individuals.

While we have been cautious not to label the developmental framework of atypical selective attention in ASD addressed in the current thesis as a “theory” akin to the theory of mind, weak central coherence (WCC) and executive dysfunction theories, it may still be helpful to evaluate the framework we have explored in a similar manner to these theories. In Chapter 1 we noted that a unified cognitive theory of ASD (or any neurodevelopmental disorder) must meet certain criteria. In particular, the implicated cognitive cause must be primary, universal, and specific. We believe that there is cause to question the primacy of WCC, as longitudinal work suggests it does not uniquely contribute to later ASD symptoms (Pellicano, 2013b). Furthermore, there is evidence to suggest that a theory of mind deficit may not be universal (e.g., Baron-Cohen et al., 1985). Finally, reports of executive dysfunction in other neurodevelopmental disorders,

including ADHD (Biederman et al., 2004), cast doubt on its specificity. So how does atypical attention fare against these criteria?

First, with regards to the primacy of atypical attention, we believe we have provided preliminary evidence to suggest it is primary to the social impairments that are the hallmark of the disorder, at both a cognitive and symptoms level. However, further work is necessary to make a stronger claim. In particular, it will be necessary to pit atypical selective attention against competing cognitive processes, and in particular executive functions due to possible developmental relationships between the two (Garon et al., 2008). This will allow us to determine if atypical attention uniquely contributes to ASD symptoms, like Pellicano (2013b) has done. Doing so will also allow for the combination of both the cognitive and symptoms levels.

Second, with regards to universality, even the most consistent selective attention finding (enhanced visual search in ASD) does not replicate in every instance (e.g., Hessels et al., 2014; Van Eylen et al., 2015). Indeed, in Chapter 3 we did not find evidence of enhanced performance in a multi-target search cancellation task, but rather *disorganized* search, to which both ASD and ADHD symptoms independently contributed. As discussed in this chapter, it is clear that task parameters are important when evaluating visual search in ASD.

Finally, with regards to specificity, there are several other neurodevelopmental disorders that present with atypical selective attention, including ADHD (Brodeur & Pond, 2001; Jonkman et al., 2004) and William's syndrome (Cornish, Scerif, & Karmiloff-Smith, 2007; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004). How can atypical selective attention contribute to the social impairments seen in ASD if individuals with William's syndrome, who present with hyper-social behaviors in contrast to ASD, demonstrate similar atypical selective attention? One explanation is

that although selective attention may play a role in several neurodevelopmental disorders, the distinguishing factor is the timing of impairments as well as their developmental trajectories, leading to differing outcomes (Cornish et al., 2007). Another explanation is that perhaps it is not solely atypical selective attention that is acting to lead to the social impairments seen in ASD, but rather a combination of multiple cognitive atypicalities/impairments. It is to this idea that we now turn.

As the review of cognitive theories of ASD in the introduction of this thesis suggests, there is unlikely to be a unitary theory of ASD. This realization is not new: as Goodman (1989) pointed out rather early in this debate, “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” (R. Goodman, 1989 pg. 410). However, there is precedence that suggests that models incorporating multiple cognitive systems can explain disorder, which has allowed for promising traction with respect to treatment.

For example, a model implicating both “hot” and “cold” cognition in depression has been posited previously (Robinson, Roiser, & Sahakian, 2016; Roiser, Elliott, & Sahakian, 2012). In this model, atypical “hot” cognition is considered to involve emotional stimuli, with depressed individuals demonstrating a “negative affective bias,” or a fixation on negative information at the expense of the positive. “Cold” cognition, on the other hand, relates to domain-general cognitive processing, including attention and memory, with depressed individuals often characterized by impairments in these cognitive processes. While “hot” cognition is typically associated with more bottom-up, sub-cortical processes and “cold” cognition is typically associated with top-down, cortical processes, the authors argue that negative affective biases in “hot” cognition demonstrate both top-down and bottom-up aspects. Crucially, within this model, having

either altered hot or cold cognition on its own is not necessarily sufficient to cause depression. Rather, the combination of these altered cognitions is what impacts the presentation of depression. Even more critically, preserved general cognitive processing/ cognitive control relative to the severity of negative affective bias promotes resilience, whereas impaired cognitive control promotes vulnerability. Furthermore, the authors argue that treatments work at differing levels—antidepressants function to correct a negative affective bias at the more bottom-up level whereas cognitive therapies address the more top-down concerns (Figure 33).

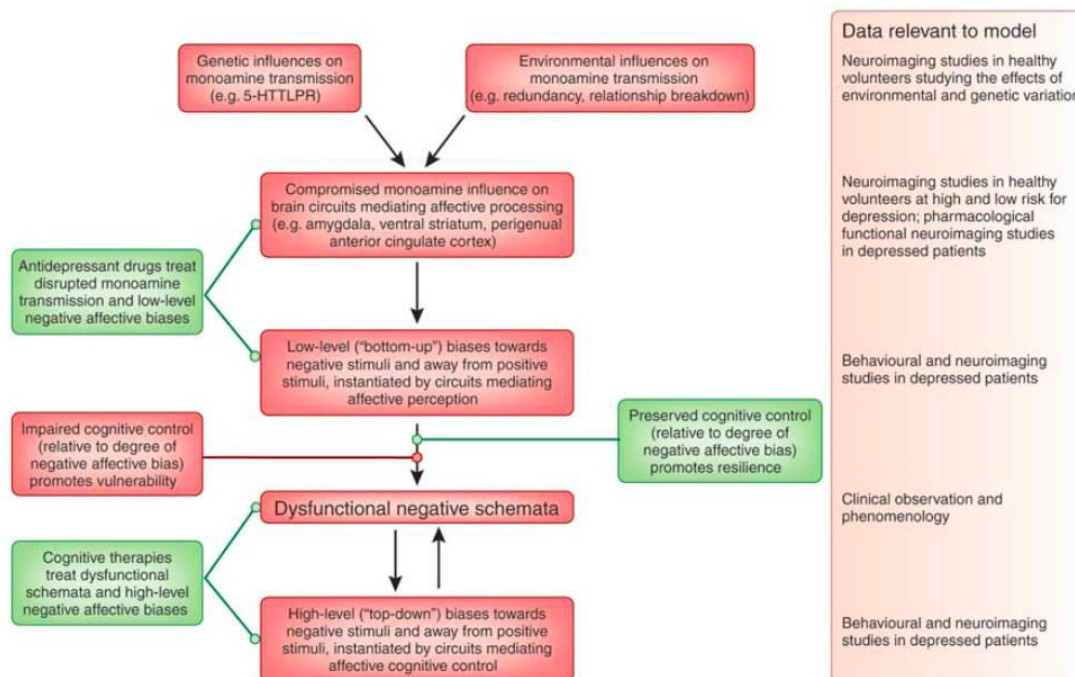


Figure 33. Depiction of the cognitive neuropsychological model of depression implicating both “hot” and “cold” cognition (taken from Roiser et al., 2012)

An alternative model

Based on the results of the current thesis as well as the previous literature, a similar model may be posited for ASD. As discussed previously, there are two broad

aspects to atypical selective attention in ASD. One is the more domain-general, non-social (“cold”) atypical attention, as seen in visual search in particular as well as other classic selective attention paradigms. The other is more domain-specific (“hot”), and can succinctly be described as an atypical social attention bias, or a lack of a social attention bias. For this second piece, there may be bottom-up and top-down aspects, similar to the model described above. For the bottom-up aspect, as discussed in Chapter 1, it is important to note that both research with infants (Cassia et al., 2004) as well as neuroimaging (Gauthier & Tarr, 1997; Tarr & Gauthier, 2000) suggest that the neurotypical attention bias towards faces and people may be driven by non-face specific mechanisms, and in particular non-face specific perceptual proclivities (Cassia et al., 2004). As low level perceptual differences are reported in ASD as young as 6 months of age (McCleery et al., 2007), and computational models suggest that what is salient for autistic individuals based on perceptual properties may not be what is salient for neurotypical individuals (S. Wang et al., 2015), it is possible that these bottom-up aspects may contribute to an atypical social attention bias in ASD. For the top-down aspect, experience over time in neurotypical individuals that pairs reward with social stimuli may result in a learned motivation and expertise that may in turn drive attention towards people and faces—learning that may be absent in autistic individuals due to reduced attention to social stimuli.

The current thesis offers some suggestive evidence of low-level perceptual differences, although limited to investigating autistic traits in neurotypical individuals. Participants with high autistic traits in Chapter 4 showed reduced looking to both social *and* non-social distractors that were equated for perceptual salience. This suggests that it is not only that individuals with high autistic traits look less at people, they look less at what is neurotypically salient in general. Indeed, those with high autistic traits still

looked more at social compared to non-social distractors. This point is not new, although perhaps not emphasized enough—early studies of gaze avoidance and social attention concluded that “in contrast to normals, autistic children look less at the experimental stimuli, but do not selectively avoid social ones” (Lovaas et al., 1971 pg. 213). Although the findings from Chapter 4 must be replicated with diagnosed autistic individuals, it is preliminary evidence that bottom-up perceptual differences may be driving reduced attention to social stimuli in ASD.

Furthermore, Chapters 4, 5 and 6 suggest that once an attention bias towards faces is established (as early as 6-10 years old in Chapter 6), this bias has the potential for cascading effects by way of memory and potentially memory-guided orienting that further reinforce this bias and may affect daily life. This may be a mechanism by which the more top-down influences on social attention (or lack thereof) develop over time.

Results from Chapters 4-6 therefore give evidence for potential top-down and bottom-up influences on the “hot” atypical social attention bias in ASD. But what of the non-social, “cold” atypical attention? By investigating longitudinal relationships between non-social attention and social functioning at both the cognitive (Chapter 2) and symptoms (Chapter 3) levels, we revealed unidirectional relationships whereby attention predicts social functioning but not vice versa over development. These findings suggest that non-social selective attention does play a role in the social impairments seen in ASD.

Given these findings, it is possible to conceive of a similar two-part model for ASD. A reduced social attention bias, driven by both top-down and bottom-up aspects, is not necessarily sufficient for an ASD diagnosis. Atypical non-social selective attention relative to the reduced social attention bias is necessary and increases vulnerability, whereas more neurotypical-like selective attention promotes resilience.

Indeed, the idea that executive functions (which are related to attention skills, as discussed previously) promotes resilience in the context of familial or other risk for ASD has been discussed in the literature (M. H. Johnson, 2012).

Importantly, this two-part model overcomes three caveats with the developmental framework of atypical attention in ASD discussed above. First, it has the potential to explain why other neurodevelopmental disorders present with atypical selective attention, yet contrasting social functioning—it is not solely atypical non-social selective attention that leads to ASD, the bottom-up and top-down influences contributing to reduced social attention are necessary as well, and these may differ in other developmental disorders. Second, it addresses the universality of atypical selective attention in ASD. In the current model it is not the overall degree of atypical non-social attention that is important, but rather the degree of atypically in relation to the degree of social attention bias. Within this framework, it is possible to conceive of instances where autistic individual do not differ at the group level in comparison to neurotypical individuals. Third, it does away with a unitary cognitive model of ASD, which is unlikely to explain the heterogeneity in the disorder, by including multiple cognitive systems. Further study could test this model by investigating low-level perceptual features, domain-general selective attention, as well as social attention over time in infants at familial risk for ASD to examine developmental relationships.

Limitations

Important to discuss is the reliability of the measures used throughout the thesis. It is possible that measurement error may be contributing to some of the null and/or unexpected findings throughout the thesis. In particular, there are two sources of measurement error to consider. The first is with the experimental measures. Although

for chapters 4-6 we are more confident in the reliability of the experimental measures, given that findings replicated across chapters, it is important to consider the reliability of the search organization measures in Chapter 2. Children could participate in a maximum of two trials per condition, and many children completed only one trial in some conditions. This was done to keep children engaged, as the cancellation task was one of a battery of tasks children were asked to complete, and more trials would have required additional sustained attention. Further studies could perhaps replicate these findings with more trials, as well as look at the consistency within participants between trials, in order to assess reliability. Another source of potential measurement error is with the questionnaires, used to assess individual differences. Although the measures included here (e.g., CBCL, Conners, SCQ, etc.) are widely used, and have been validated in the literature, it is nonetheless important to assess reliability within particular samples utilizing tools such as Cronbach's alpha. This was not done in the current thesis, and therefore serves as a limitation.

Further study

One area for further study is to more causally investigate the relationship between atypical non-social selective attention and social impairment in ASD. Although longitudinal data better addresses causal hypotheses than cross-sectional data, by capitalizing on the fact that causes must come before effects, it still does not address the concern that some third, unobserved variable may be the causal agent. A more ideal way to address causal hypotheses is intervention. For example, a future study could implement attention training in young infants to see if training improves social cognition. Cognitive training is a subject of intense debate, however, particularly with regards to transfer (Melby-Lervåg & Hulme, 2013), and therefore should be approached

with caution. Another example is using medication that improves attention, such as the ADHD medication methylphenidate, and measuring its effects on social impairments over time, as suggested in Chapter 3.

An obvious area of further study would be to use the same experimental paradigm developed in Chapters 4-6 with individuals with ASD. Although we demonstrate an effect of individual differences in the autism-spectrum quotient (AQ: Baron-Cohen et al., 2001) in Chapter 4, including adults and children with a full ASD diagnosis and comparing them to neurotypical individuals may give more concrete evidence of differences relevant to ASD.

Conclusion

The work presented here for the first time examined longitudinal relationships between the non-social atypical attention seen in ASD and the social impairments that are the hallmark of the disorder, as well as a potential mechanism through which atypical social attention in particular may have cascading effects on social impairment through learning and memory. These findings have implications for the development of therapeutic and educational programs for autistic individuals that capitalize on their unique cognitive profile of strengths as well as weakness. Importantly, the experimental work presented here has allowed us to posit a two-part model for ASD that addresses concerns with an atypical selective attention framework of ASD, with testable hypotheses for further study.

Appendix I

Overall effects of categorical and perceptual demands on search accuracy and speed

Non-parametric Friedman's tests were used due to high skew, with one within-subjects factor (condition: exemplar, categorical, and perceptual). There were significant main effects of search condition for each measure. As this procedure does not allow for missing data, these analyses were restricted to those children who completed all three conditions: 17 LR and 80 HR children.

For **accuracy**, there was a main effect of condition, $\chi^2(2) = 34.48$, $p < 0.001$. Wilcoxon signed-rank tests revealed that this effect was driven by Bonferroni-corrected significant differences between categorical search and both exemplar search ($p < 0.001$) and perceptual search ($p < 0.001$), with lower accuracy in categorical search, and no significant difference between exemplar and perceptual search ($p = 0.156$) (Table 1).

Table 1
Measures of search quality and organization across conditions

Measure	Condition		
	Categorical	Exemplar	Perceptual
Accuracy	16.69 (0.40)	17.80(0.25)	17.56(0.28)
Errors	6.58(1.00)	1.79(0.68)	2.74(0.62)
Time to completion (s)	66.99(5.25)	35.54(3.65)	42.12(4.89)

Figures in parentheses are 95% confidence intervals. Sample limited to those children who contributed data for all three conditions.

For **errors**, there was a main effect of condition, $\chi^2(2) = 71.70$, $p < 0.001$. Wilcoxon signed-rank tests revealed this effect was to be driven by Bonferroni-corrected significant among all conditions ($p < 0.001$), with the most errors in categorical search, then perceptual search, and then exemplar search (Table 1).

For **time to completion**, there was a main effect of condition, $\chi^2(2) = 98.31, p < 0.001$. Wilcoxon signed-rank tests revealed this effect was driven by Bonferroni-corrected significant differences among all conditions ($p < 0.001$ for differences between categorical and perceptual/exemplar search; $p = 0.006$ for the difference between perceptual and exemplar search), with the longest time to completion for categorical search, then perceptual, then exemplar (Table 1).

ASD and ADHD symptoms as predictors of search accuracy and speed

ANCOVAs could not be carried out on **accuracy**, **errors**, or **time to completion** due to extreme skew. However, non-parametric correlations with MSEL, ADOS-SA, ADOS-RRB, and CBCL-ADHD were run for all participants (Table 2) and high risk participants (i.e., excluding cases fully diagnosed with ASD) separately (Table 3). This analysis yields similar findings to that of the Q score.

Table 2

Spearman's rho non-parametric correlations between traditional search measures and ASD/ADHD symptoms and MSEL for all participants.

		Accuracy			Errors			Time to completion (s)		
		E	P	C	E	P	C	E	P	C
ADOS-SA	r	-0.073	0.149	-0.171	0.141	-0.135	0.140	0.078	-0.028	0.154
	Sig.	0.437	0.115	0.052	0.130	0.154	0.112	0.405	0.769	0.080
	N	116	113	130	116	113	130	116	113	130
ADOS-RRB	r	-0.010	-0.116	-0.198	0.153	0.191	0.223	0.182	0.112	-0.010
	Sig.	0.912	0.222	0.024	0.100	0.043	0.011	0.051	0.238	0.911
	N	116	113	130	116	113	130	116	113	130
MSEL	r	0.280	0.215	0.490	-0.395	-0.319	-0.572	-0.350	-0.188	-0.320
	Sig.	0.002	0.022	0.000	0.000	0.001	0.000	0.000	0.046	0.000
	N	116	113	130	116	113	130	116	113	130
CBCL-ADHD	r	-0.072	-0.063	-0.097	0.229	0.240	0.183	0.175	0.019	0.049
	Sig.	0.459	0.526	0.290	0.017	0.014	0.045	0.070	0.850	0.595
	N	108	104	120	108	104	120	108	104	120

E = exemplar search, P = perceptual search, C = categorical search. Mullen Scales for Early Learning, Early Learning Composite (MSEL); Autism Diagnostic Observation Schedule, Social Affect (ADOS-SA); Autism Diagnostic Observation Schedule, Restricted and Repetitive Behaviors (ADOS-RRB); Child Behavior Checklist, ADHD t-scores (CBCL-ADHD). Cells shaded in grey highlight statistically significant correlations.

Table 3

Spearman's rho non-parametric correlations between traditional search measures and ASD/ADHD symptoms and MSEL for HR participants only.

		<u>Accuracy</u>			<u>Errors</u>			<u>Time to completion (s)</u>		
		E	P	C	E	P	C	E	P	C
ADOS-SA	r	-0.016	0.131	-0.085	0.175	-0.139	0.094	0.080	0.010	0.137
	Sig.	0.886	0.245	0.425	0.116	0.218	0.378	0.474	0.928	0.195
	N	82	80	91	82	80	91	82	80	91
ADOS-RRB	r	0.014	-0.021	-0.107	0.119	0.158	0.144	0.102	0.115	-0.178
	Sig.	0.902	0.851	0.311	0.287	0.161	0.174	0.364	0.311	0.091
	N	82	80	91	82	80	91	82	80	91
MSEL	r	0.304	0.229	0.428	-0.347	-0.311	-0.518	-0.254	-0.146	-0.270
	Sig.	0.005	0.041	0.000	0.001	0.005	0.000	0.021	0.195	0.010
	N	82	80	91	82	80	91	82	80	91
CBCL-ADHD	r	-0.029	-0.128	-0.111	0.316	0.227	0.142	0.102	-0.084	-0.056
	Sig.	0.801	0.282	0.316	0.005	0.053	0.198	0.383	0.481	0.613
	N	76	73	84	76	73	84	76	73	84

E = exemplar search, P = perceptual search, C = categorical search. Mullen Scales for Early Learning, Early Learning Composite (MSEL); Autism Diagnostic Observation Schedule, Social Affect (ADOS-SA); Autism Diagnostic Observation Schedule, Restricted and Repetitive Behaviors (ADOS-RRB); Child Behavior Checklist, ADHD t-scores (CBCL-ADHD). Cells shaded in grey highlight statistically significant correlations.

Important to note: the sample sizes of Tables 2 and 3 demonstrate the varying numbers of conditions completed across participants.

Relationships between covariates and dependent measures

To investigate the relationship between covariates used in the main analyses, as well as the three dependent measures, non-parametric correlations were run (Table 4, Table 5).

Table 4

Spearman's rho non-parametric correlations between covariates for all participants

		ADOS-SA	ADOS-RRB	MSEL	CBCL-ADHD
ADOS-SA	r		0.223	-0.26	0.027
	Sig.		0.01	0.003	0.765
	N		131	131	121
ADOS-RRB	r	0.223		-0.234	0.301
	Sig.	0.01		0.007	0.001
	N	131		131	121
MSEL	r	-0.26	-0.234		-0.203
	Sig.	0.003	0.007		0.026
	N	131	131		121
CBCL-ADHD	r	0.027	0.301	-0.203	
	Sig.	0.765	0.001	0.026	
	N	121	121	121	

Mullen Scales for Early Learning, Early Learning Composite (MSEL); Autism Diagnostic Observation Schedule, Social Affect (ADOS-SA); Autism Diagnostic Observation Schedule, Restricted and Repetitive Behaviors (ADOS-RRB); Child Behavior Checklist, ADHD t-scores (CBCL-ADHD). Cells shaded in grey highlight statistically significant correlations.

Table 5

Spearman's rho non-parametric correlations between measures averaged across conditions for all participants

		Q score	Best R	Intersections rate
Q score	r		0.107	-0.237
	Sig.		0.222	0.006
	N		131	131
Best R	r	0.107		-0.398
	Sig.	0.222		0.000
	N	131		131
Intersections rate	r	-0.237	-0.398	
	Sig.	0.006	0.000	
	N	131	131	

Cells shaded in grey highlight statistically significant correlations.

Excluding HR-ASD from dimensional analyses

In order to determine if the children with an ASD diagnosis were driving the relationships described in the main text, all three mixed effects models were re-run excluding those children who received an ASD diagnosis.

For **Q score**, our index of overall search efficiency, there were no differences from the previous analysis. There was a significant effect of condition, $F(2, 89.42) = 91.08, p < 0.001$. There was also a significant effect of MSEL, $F(1, 101.44) = 23.95, p < 0.001$, with higher mental development related to higher Q scores (greater speed and accuracy). In addition, there was a condition by ADOS-SA interaction, $F(2, 93.12) = 3.18, p = 0.05$.

For **best R**, our index of spatial systematicity, there were no differences from the previous analysis. There was a significant main effect of condition, $F(2, 92.49) = 6.88, p = 0.002$. There was also a significant main effect of CBCL-ADHD, $F(1, 96.39) = 10.60, p = 0.0028$, with higher ADHD symptom severity related to lower best R (more spatially unsystematic search).

For **intersections rate**, our index of spatial organization, there were no differences from the previous analysis. There was a significant main effect of condition, $F(2, 94.22) = 11.68, p < 0.001$. There were also significant main effects of three of the covariates: ADOS-SA, $F(1, 106.06) = 7.04, p = 0.009$, ADOS-RRB, $F(1, 100.68) = 5.76, p = 0.02$, CBCL-ADHD, $F(1, 99.29) = 11.68, p < 0.001$, with higher scores related to higher intersections rates (i.e., more disorganized search). The main effect of ADOS-RRB was further qualified by an ADOS-RRB by condition interaction, $F(2, 95.82) = 3.20, p = 0.05$.

Indices of “categorically systematic” search

In the categorical search condition, it was possible for children to use a particular strategy of first touching all of the cats, then all of the dogs, then all of the camels, etc. This strategy of selection of each basic level in “runs” is found in animals selecting prey in the wild when prey are hard to detect compared to those that pop-out, as well as in humans during a cancellation foraging task when targets are complex (conjunctive search) compared to simple targets (feature search) (Kristjánsson, Jóhannesson, & Thornton, 2014). This strategy might also reflect on the representation of the global “animal” category as a collection of “basic level” categories rather than a unitary concept. In order to investigate if children in the current study were using this strategy, and if this strategy related to ASD or ADHD symptoms, we calculated the number of runs children made during the categorical search condition. Runs consisted of consecutive touches of the same target type (cats, dogs, etc.), such that fewer runs meant search focused on basic category types, while more runs meant more frequent switching between basic categories. If children sampled all basic categories, the minimum number of runs was five due to there being five target types and the maximum was 18 if the child touched all the targets possible and never the same target type consecutively. As children varied in the number of targets they touched, number of runs was divided by the number of target touches. Non-parametric correlations were run between this scaled run length and ADOS-SA, ADOS-RRB, MSEL, CBCL-ADHD as well as with Q score, best R and intersections rate for categorical search. In average, LR participants made 0.86 runs (SD 0.09) and HR participants made 0.85 runs (SD 0.07) (difference) Interestingly, ASD symptoms did not relate to this measure but there was a negative correlation with CBCL-ADHD, $r(120) = -0.25$, $p = 0.006$, with higher ADHD symptoms related to fewer runs (i.e., fewer switches across target types, and therefore

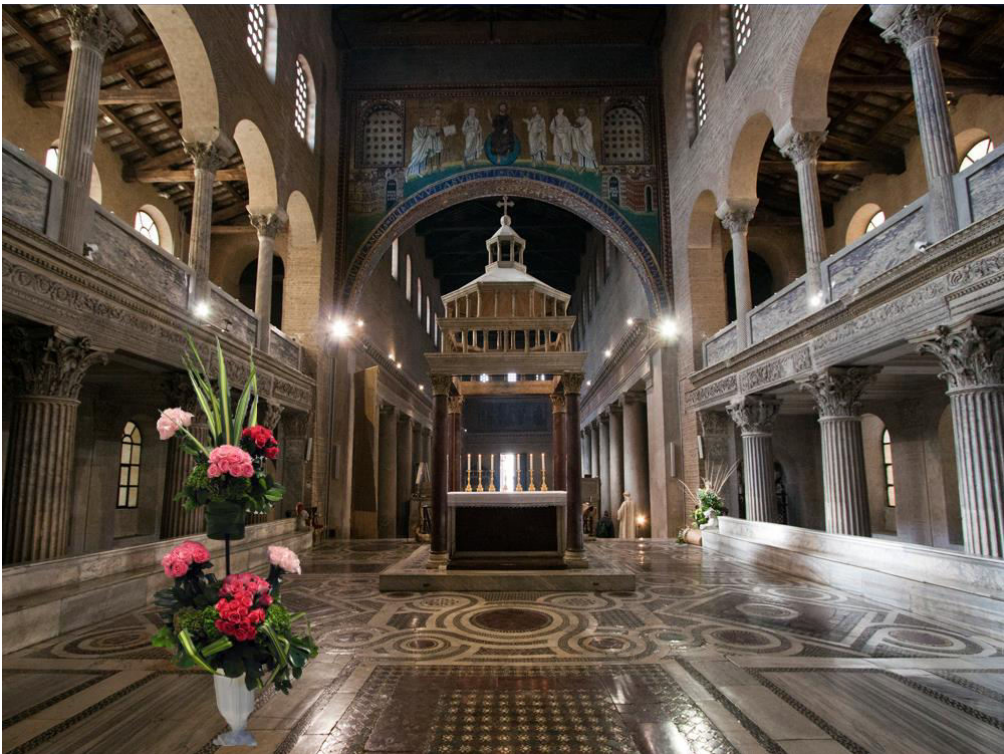
exemplar-based search), and no correlations with MSEL. It is possible that adopting this strategy mainly reflects poor executive control, in particular the ability to shift between categories, akin to task shifting. There was also a positive correlation between run length and Q score, $r(130) = 0.27, p = 0.002$, with more runs (i.e., more switches across target types) related to better search efficiency, and a negative correlation with intersections rate, $r(130) = -0.35, p < 0.001$, with more runs (i.e., more switches across target types) related to less disorganized search.

Appendix II

Example stimuli for Chapters 4-6







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