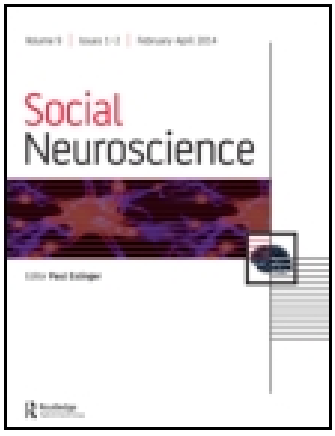

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A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders

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A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders

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Aberrant eye gaze mechanisms have been implicated in autism spectrum disorders (ASD). Studies of eye movements in children with ASD reveal diminished eye gaze duration and lack of specific eye gaze fixation to the eyes and/or mouth compared with controls. However, findings to date have been contradictory. We examined eye-tracking studies on face processing in children with ASD and conducted meta-analyses to examine whether these children demonstrate atypical fixation on primary facial regions. Twenty eye-tracking studies in children with ASD were reviewed, of which the results from 14 studies were incorporated in the meta-analyses that evaluated fixation duration on (i) eyes (eight studies) and (ii) mouth (six studies). The results reveal that children with ASD have significantly reduced gaze fixation to the eye region of faces. The results of the meta-analyses indicate that ASD patients have significant impairments in gaze fixation to the eyes. On the other hand, no significant difference was uncovered in terms of fixation to the mouth region; however, this finding needs to be interpreted with caution because of the significant heterogeneity in the mouth fixation studies. The findings of this meta-analysis add further clarity to an expanding literature and suggest that specific eye gaze fixation to the eye region may represent a robust biomarker for the condition. The heterogeneity associated with the mouth fixation data precludes any definitive statement as to the robustness of these findings.

Keywords: ASD; Children; Eye-gaze; Face-processing; Fixation; Meta-analysis.

Autism spectrum disorders (ASD)

Initially described by Kanner, in 1943, autism is a pervasive developmental disorder, expressed across multiple disciplines (Boraston & Blakemore, 2007; Kanner, 1968; Katarzyna, Fred, & Ami, 2010). It has been characterized by three main features: (1) deficits in reciprocal social interactions; (2) atypical development and use of language; and (3) repetitive behaviors accompanied by a confined diversity in interests and activities (APA, 2013; Kanner, 1968; Katarzyna et al., 2010). ASD is presently considered a common and often severe developmental disorder, from behavioral, neurobiological, genetic and cognitive aspects (APA, 2013; Klin & Mercadante, 2006). More recent studies also highlight comorbidities commonly associated with ASD, such as epilepsy, anxiety and mood disorders (Lecavalier, 2006; Tuchman & Rapin, 2002).

Established conceptualizations of ASD have indicated that the emergence of its symptomatology ranges from the first 6 months (Jones & Klin, 2013) to the first 2 years of life, presents in one of two ways: (1) "early onset" or (2) "regressive autism" (Ozonoff et al., 2008). A series of miscellaneous cases have

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been described, where some individuals exhibit a developmental plateau that fails to advance while others exhibit assorted symptoms such as early delays accompanied by a simultaneous loss of skills (Ozonoff et al., 2008). Notwithstanding its onset, ASD appears and develops within the first 3 years of life and its median age of diagnosis is around 5 years (APA, 2013; Jones, Carr, & Klin, 2008).

Atypical eye mechanism in children with ASD

From the neonatal stage, the eyes act as receptors and conveyors of social cues (Norbury et al., 2009). Gaze direction is a rapid and automatic process that triggers reflexive shifts in visual attention (Watanabe, Miki, & Kakigi, 2002). Thus, gaze direction (normal or aberrant) impacts emotional responses, social attention, and the downstream face perception in humans (Langton, Watt, & Bruce, 2000; Watanabe et al., 2002). In ASD, the mechanisms that underpin the ability to direct gaze to a specific stimulus (social or nonsocial) and hence the capturing of attention are atypical (Jones et al., 2008), thus profoundly impacting childhood development. Such aberrant eye gaze behavior may not necessarily be a result of oculomotor dysfunction in ASD, but rather neurobiological factors that influence what eye movements are directed toward.

Behavioral studies of eye movements comparing ASD to neurotypically developing children have identified patterns of preferential looking as core diagnostic signs of ASD (Jones et al., 2008). Neurotypically developing children preferentially look people in the eyes; however, children with autism prefer to orient their eye gaze on less socially relevant aspects of their surroundings, and this is often accompanied by sensory-oriented behaviors (Jones et al., 2008; Zwaigenbaum et al., 2005). These are often exhibited in stereotyped, self-stimulatory behaviors (Zwaigenbaum et al., 2005).

The robustness of the aforementioned characteristic eye gaze abnormalities in ASD has been proposed to have a predictive value in establishing a diagnosis (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Zwaigenbaum et al., 2005). According to this notion, the more dominant the fixation is on parts of the face or body (aside from the eyes), the more likely that a child may be on the autism spectrum and the more severe the social disability (Jones et al., 2008; Klin et al., 2002).

Brain mechanism associated with atypical eye mechanisms in children with ASD

The last decade has seen significant advances in our understanding of the brain mechanisms and neural circuitry that underpins social cognition and perception (Pelphrey & Carter, 2008). The sophisticated neuroimaging techniques that have probed brain structure, function, and neurochemistry have contributed to these advances and revealed a series of neural substrates, networks, and pertinent neurotransmitter systems that are crucial to the development of a novel theoretical framework for understanding the workings of the social brain (Pelphrey & Carter, 2008).

According to research, mechanisms that result in atypical eye gaze following face processing (Volkmar & Juraska, 2011) arise from dysfunctions across a range of brain regions that include the amygdala (Adolphs, Baron-Cohen, & Tranel, 2002; Adolphs, Tranel, Damasio, & Damasio, 1995; Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Kawashima et al., 1999), frontal eye fields (FEF) (Agam, Joseph, Barton, & Manoach, 2010), temporal parietal junction (Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011), insula (Critchley et al., 2000; Morris, Ohman, & Dolan, 1999; Phillips et al., 1997; Sprengelmeyer et al., 1996), and the dorsal lateral prefrontal cortex (Senju & Johnson, 2009a). There is now an expanding neuroimaging literature examining specific brain regions and their relative contributions to abnormal eye movements in ASD. For example, the right middle portion of the fusiform gyrus (FG) has been specifically highlighted for its significance in face perception (Allison, Mccarthy, Nobre, Puce, & Belger, 1994; Kanwisher, Mcdermott, & Chun, 1997) in typically developing children. Research findings suggest that increased activation of the FG area indicates enhanced face encoding (Senju & Johnson, 2009b). The lateral aspect of the FG, also referred to as the "fusiform face area" (FFA), plays an important role in structural face encoding in the environment as well as in rapid face recognition (Kanwisher et al., 1997; Kleinhans et al., 2008; Pelphrey & Carter, 2008; Volkmar & Juraska, 2011). Activation in the FFA of neurotypical individuals is twice as strong when subjects are presented with face stimuli rather than everyday objects, such as a chair or table (Kanwisher, 2000; Slotnick & White, 2013) supporting the notion that this aspect of the FG specifically mediates face processing. As a result, it was initially speculated that atypical development of the FFA, in correlation with diminished activation to faces in this

area of the brain, significantly contributed to face processing deficits in ASD populations (Dalton et al., 2005; Schultz et al., 2000). A recent study employing a face recognition task has reported significantly diminished activity in the FFA in ASD subjects when contrasted to controls (Volkmar & Juraska, 2011). However, despite its activation in response to facial stimuli, the FFA can also activate to nonfacial stimuli too (Slotnick & White, 2013). The latter reflects the fact that FFA activation is linked to both faces and nonface (i.e., shapes) features, highlighting a mediating role in the left and central visual fields (Slotnick & White, 2013). Furthermore, a converging body of research has failed to uncover significant changes in the FFA, implicating that aberrant face processing in ASD is not a simple dysfunction of the FFA but rather a complex anomaly in the extended neural network involved in social perception and cognition (Bird, Catmur, Silani, Frith, & Frith, 2006; Dapretto et al., 2006; Hadjikhani et al., 2004). Kleinhans et al. (2008) reported similar patterns of activation and location of activation for both ASD and controls, concluding that FFA activation is neither correlated with atypical heterogeneous nature of the face processing in ASD, nor with compromised sensitivity to faces. Further studies have indicated that differences in FFA activation were subsequent to: (1) task demands (Piggot et al., 2004; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004); (2) familiarity (Pierce, Haist, Sedaghat, & Courchesne, 2004); or (3) duration of fixation on the eye region (Dalton et al., 2005). Taken together, the ambiguity of findings at present makes the need for further investigation of the FFA in ASD imperative.

Another brain region that has received considerable attention in recent years has been the amygdala. The amygdala is activated when implicitly processing expressions of emotions and is integral to the modulation of social and emotional behavior (Morris et al., 1996). Given its role in the processing of emotion, unsurprisingly, it is also activated when interpreting face and social cues (Bonda, Petrides, Ostry, & Evans, 1996; Kawashima et al., 1999; Senju & Johnson, 2009a) and in this regard strong correlations have been reported in face paradigms that have contained emotionally provocative stimuli (Adolphs et al., 2002; Volkmar & Juraska, 2011). Moreover, the amygdala contains rich interconnections with frontal and limbic regions both of which are also implicated in the analysis of facial expressions to determine emotional states (Adolphs et al., 1995). It has been suggested that deficits seen in the amygdalo-hippocampal complex may partly account for social impairments in ASD as both regions are structurally altered in autism (Critchley et al., 2000; Schumann et al., 2004).

The superior temporal sulcus (STS) is also putatively involved in the processing of dynamic expressions of emotions as well as in the translation of others' actions and intentions using biological motion cues (Bonda et al., 1996; Labar, Crupain, Voyvodic, & Mccarthy, 2003; Pelphrey, Morris, & Mccarthy, 2004; Pelphrey, Singerman, Allison, & Mccarthy, 2003; Pelphrey, Viola, & Mccarthy, 2004; Pelphrey et al., 2003). More recently, Pelphrey and Carter (2008) reported that impairments in the STS are associated with the level of social impairment.

Activity in other brain regions including the cerebellum, mesolimbic structures, and the temporal lobe has also been reported to differ in ASD subjects, relative to controls, in facial expression tasks (Critchley et al., 2000). Finally, aberrant activity in the medial temporal lobe, striatum, and insula has also been implicated in facial expression processing deficits in ASD (Critchley et al., 2000), a finding that is corroborated by several previous studies (Morris et al., 1999; Phillips et al., 1997; Sprengelmeyer et al., 1996).

The vast majority of studies on face recognition in ASD individuals have investigated teenagers and adults (Bradshaw, Shic, & Chawarska, 2011; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011) even though the development of face recognition skills and social engagement commences in the early months of life (Bradshaw et al., 2011). Attention to the face, as well as the processing of facial features, is considered to be among the first expressions of these skills (Bradshaw et al., 2011). Despite most eye-tracking studies not focusing on children with ASD in their early years, behavioral studies have shown that the onset age for atypical visual attention is within the first year (Ozonoff et al., 2008).

Eye gaze studies involving young ASD children have typically employed static photographs and/or color pictures. In these studies, children were presented with social and nonsocial stimuli in a static form with the objective to measure attendance and response to either condition. More recent studies have employed more sophisticated audiovisual and biological motion paradigms. It has been suggested that the emotional expressions presented via audiovisual and biological motion paradigms are less ambiguous, thus resulting in more robust findings. It has been posited that this is due to a more naturalistic experience that allows actions to naturally unfold to social events (Falck-Ytter & von Hofsten, 2011). Audiovisual stimuli presently account for the majority of methods employed in eye-tracking studies of ASD in children. They are generally preferred as they

provide richer insight to behavior mechanisms due to their dynamic and ecological effect in comparison to static photos and cartoon-like images (Falck-Ytter & von Hofsten, 2011).

More recently, there have been several studies that have acquired eye gaze in real time during actual social interactions (Falck-Ytter & von Hofsten, 2011). Data collected in real-time, naturalistic social settings have advantages over traditional paradigms that have employed static photographs as it allows for a better characterization of eye gaze abnormalities since the social interactions are more representative. However, these techniques are not without limitations, which may impact on the final study results. The main limitation of such techniques relate to the presence of the camera that acquires the eye gaze signal and is mounted on a frame that is in turn located on the subject's head. Given that children with ASD often present with comorbid anxiety, the prominent nature of the equipment may result in increased anxiety and as a result encourage a "downcast gaze" phenomenon (Noris et al., 2011, 2012).

Presently, the literature on eye movement studies in ASD suggests a lack of consistency in the approaches to data collection, analysis, and subsequently, interpretation of the findings. As a consequence, this has led to a number of contradictory findings and the lack of an overall consensus on the interpretation of these changes. The aim of this systematic review and meta-analyses was to examine the methods and results of the currently available eye movement studies in ASD and to ascertain whether children with ASD have significantly abnormal eye gaze responses to the mouth and eye regions.

SYSTEMATIC REVIEW

Methods

A literature search for papers published in English was conducted via PubMed, MedLine, Embase, PsycINFO, and ScienceDirect on 21 April 2013 using the following keywords combined with autism spectrum disorders: "infants," "toddlers," "children," "eye tracking," "face processing."

Our initial literature search yielded 35 articles on eye-tracking studies in children with ASD. Of these 35 articles, 20 met eligibility criteria and were included for systematic review (see Table 1).

Eligibility criteria were as follows: (1) patient group had a diagnosis of high/low functioning autism disorder, Asperger's syndrome or pervasive developmental disorder-not otherwise specified; (2) control groups included neurotypically developing children, unaffected siblings, children classified as high or low risk for autism, as well as developmentally delayed children; (3) experimental paradigms to measure face processing, attendance and response to social and nonsocial stimuli, were presented to an eye-tracking screen; (4) measurements included time and number of fixation to the regions of the eyes and mouth compared to nonsocial stimuli; (5) the mean age of participants was 16 years or below.

Experimental designs and stimuli utilized in eye-tracking studies

The studies included in this systematic review employed a range of experimental designs that included (1) static photographs and pictures (Anderson et al., 2006; Bradshaw et al., 2011; Chawarska & Shic, 2009; Dalton et al., 2005; Key & Stone, 2012; van der Geest, Kemner, Verbaten, et al., 2002; Wilson et al., 2010); (2) dynamic audio-visual stimuli (Hosozawa et al., 2012; Jones et al., 2008; Nakano et al., 2010; Shic et al., 2011); (3) digitized stimuli exported from films (Speer et al., 2007); (4) digitized color video clips (Norbury et al., 2009); (5) point light animations of biological motion (Klin et al., 2009); (6) naturalistic images (Noris et al., 2012); (7) semi-structured live interactions (Noris et al., 2011); (8) free-viewing tasks (Chawarska et al., 2013); (9) free viewing of dynamic social scenes (Rice et al., 2012); (10) scanning of social stimuli (Dalton, Nacewicz, Alexander, & Davidson, 2007); and (11) cartoon-like images containing social and nonsocial stimuli (van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2002). Taking into account the technical approach of the aforementioned studies in conjunction with the study findings, this review has been arranged in types of stimuli/techniques employed by the eye-tracking studies that met the inclusion criteria.

Eye gaze patterns in children with ASD

van der Geest, Kemner, Verbaten, et al. (2002) conducted two studies on gaze behavior involving human faces and examined gaze fixation times. In the first study, the stimuli were composed of faces with emotional expressions, and in the second, faces with neutral expressions were in different orientations. Interestingly, the first study showed that both neurotypically developing and children with ASD exhibit the same fixation duration for upright faces with or

TABLE 1
Tabulation of eye-tracking studies in children with ASD reviewed (highlighted: studies included in the meta-analysis)

		Mean age		*Gender (M)*					
N	*Authors*	*ASD*	*C*	*ASD*	*C*	*Stimuli type*	*Measures*	*Principal findings*	*Interpretation*
1	(Anderson, Colombo, & Jill Shaddy, 2006)	46.9 M	49.8 M (TD)	*N* = 9, 8 M	*N* = 9, 8 M	Still color photographs	Fixation time: landscapes, toys, animal/ children faces	ASD group showed pupillary construction to children's faces, while controls showed pupillary dilation. Visual scanning responses to landscapes had a negative correlation with behavior subscale of ADOS- ASD	Could not determine whether differential responses were specific to one particular age or age range. Potential use of these measures as early markers of ASD.
2	(Bradshaw et al., 2011)	39 M	36 M	*N* = 21, 19 M	*N* = 12, 11 M	Color images of (1) affectively neutral female faces, (2) common objects and (3) geometric block patterns	Fixation time: objects, blocks, faces	ASD groups exhibited difficulties encoding and recognizing faces, compared to TD. ASD groups adept in encoding and recognizing objects and block patterns, reflecting a specific social impairment and a specific advantage for complex nonsocial stimuli (nonsocial visual processing advantage)	Young children with ASD exhibit: (1) specific impairments in face recognition and (2) may exhibit advantage over TD controls when processing complex nonsocial stimuli. Implications for ineffective processing of complex and high socially relevant stimuli. Pivotal need for early intervention (for later development of social info and attention), given that impairment appear so early in life.
3	(Chawarska, Macari, & Shic, 2013)	6.47 M	6.15 (LR-TD)	*N* = 12, 64%M	*N* = 35, 55%M	Free viewing task with multimodal stimuli in four conditions	Fixation time: scene, person, objects, face, eyes, mouth	Infants later diagnosed with ASD, compared to controls: (1) attended less to social scene; (2) in case of attendance, spent less time monitoring actress in general, and face in specific; (3) limited attention to actress and her activities, was not accompanied by enhanced attention to objects. All infants spent more time looking at the eyes in the two social bid conditions, in comparison to objects.	Highlighted continuity of social attention deficits in ASD and continuity in evolution of the deficits, from a limited attunement to more specific deficits in interaction and communication. First study to demonstrate prodromal behavioral features involving ASD at 6 months: (1) diminished ability of spontaneous attendance to people and their activities; (2) limited attentional bias toward people early in development: possible detrimental impact on social brain networks specialization and the generation of social interaction patterns. Likelihood of identifying phenotypic linked to visual attention for ASD diagnosis in the first year.

4	(Chawarska & Shic, 2009)	(1) *N* = 26.9 M (2) 46.4 M	(1) *N* = 26.3 M (2) 46.3 M	*N* = 44, 84%M	*N* = 30, 71%M	KDEF color pictures of affectively neutral female faces	Fixation time: eyes, mouth, nose, cheeks/ forehead, hair, neck/ body, background Inner/outer/non face	TD toddlers at both age levels (2 and 4 years) scanned visual scenes and recognized faces similarly. Toddlers with ASD: (1) looked increasingly away from faces; (2) atypically attended to key face regions; and (3) showed impaired face recognition.	Face processing in ASD may be early affected and further compromised with age development. Deficits in: (1) recognition associated with imbalanced attention among key face features; (2) face processing to impact the ability of toddlers with ASD in engaging and developing social relationships. Hence, the highlighted significance for intervention. Simply looking is not a firm implication of effective assessing/ processing of facial identity.
5	(Dalton et al., 2007)	14.4 Y	14.16 Y Sib: *N* = 13.10 Y	*N* = 12	*N* = 12 Sib: *N* = 10	Face recognition task (photos: familiar/ unfamiliar faces)	Fixation time: familiar and unfamiliar faces	Robust differences in gaze fixation while viewing images of human faces in unaffected siblings, compared to TD controls. Siblings and ASD groups spent significantly less time fixating the eye region in response to naturalistic photographs of familiar and unfamiliar faces. Siblings' gaze patterns similar to ASD group.	Eye fixation likely to be a useful quantitative behavioral/phenotypic trait to determine genetic and environmental contributions to ASD social impairments. Evidence for differences in social/ emotional processing, underlying genetic predisposition and neural circuitry in first degree relatives of children with ASD.
6	(Dalton et al., 2005)	(1) 15.9 Y (2) 14.5 Y	(1) 17.1 Y (2) 14.5 Y	(1) *N* = 14 M (2) *N* = 16 M	(1) *N* = 12 M (2) *N* = 16 M	Study 1. Facial emotion discrimination task Emotional and neutral faces from KDEF set. Study 2. Facial recognition task: familiar/unfamiliar photo	Fixation time and number: human figure, neutral objects	Variation in eye fixation in children with ASD Studies 1 and 2: (1) ASD group spent significantly less time fixating on the eyes, compared to TD controls, (2) no profound group differences in fixation time on mouth or face in general.	Compromised gaze fixation in ASD group may reflect reduced overarousal to social stimuli.

(*Continued*)

TABLE 1
(Continued)

		Mean age		Gender (M)					
N	*Authors*	*ASD*	*C*	*ASD*	*C*	*Stimuli type*	*Measures*	*Principal findings*	*Interpretation*
7	(Hosozawa, Tanaka, Shimizu, Nakano, & Kitazawa, 2012)	58.3 M	37.7 M SLI: 30.1 M	*N* = 25 21 M	*N* = 25, 14 M SLI: N = 16, 11 M	12 short videoclips of individuals engaging in social interaction	Fixation time: eyes, mouth, face, mouth/face	ASD children, compared to TD controls, exhibited: (1)atypical gaze patterns; (2) less interested and attentive to social stimuli (faces and social context); (3) viewed faces less frequently throughout a scene and; (4) shifted their gaze out of the context of scene, while TD naturally shifted gaze from one speaker to another and fixated on speaker until end of speech (eyes and mouth).	Eyes provide abundant information on emotion, identity and social phenomena. Children viewed: (1) eyes to collect social and emotional info; and (2) mouth to collect visual info related to speech. Limited time spent at eye region while viewing speech communication, may lead to less social and emotional information obtained from eyes, implying generation of misunderstandings and poor social communication skills in the future.
8	(Jones et al., 2008)	2.28 Y	2.03 Y DD: 2.06 Y	*N* = 15, 11 M	*N* = 36, 24 M DD: *N* = 15, 11 M	10 video clips of actress looking directly into camera, engaging viewer	Fixation time: eyes, mouth, body, object	ASD children exhibited significantly decreased looking at eyes and increased looking at mouth, compared to TD and DD controls. TD and DD not different in fixating patterns. Fixation on eyes by children with ASD linked to level of social disability: less fixation on eyes predicted greater social disability.	Significantly poor social development with profound consequences in social adaptation in life, indicate a likely biomarker for quantifying the manifestation of the condition at early developmental stage of toddlers with ASD. Fixation on the eyes as the most profound predictor of membership in ASD group. Reduced fixation on eyes predicted greater levels of social disability. Evidence that toddlers with ASD are deprived of an early generating bias toward preferential attention to the eyes of approaching subjects. Implications for (1) more progressively complex social interactions that follow diminished mutual gaze, gaze following and language acquisition; and (2) atypical manifestation of social mind and brain.

9	(Key & Stone, 2012)	HR-ASD 9.19 M	AR-ASD 9.01 M	*N* = 15, 9 M	*N* = 20, 13 M		Fixation time and number: eyes, mouth, face, hair, body, background, eyes and mouth	Eye-tracking data did not reveal any group differences in face-scanning behavior of AR and HR infants. No significant group differences or stimulus related effects for duration or number of fixations and total looking time.	Lack of group differences not surprising, given literature indicating 12 months as the starting point of behavioral ASD symptoms.
10	(Klin, Lin, Gorrindo, Ramsay, & Jones, 2009)	2.05 Y	2.05 Y	*N* = 21	*N* = 39 TD DD: *N* = 16	10 point light animations of biological motion with audio	Fixation time: upright and inverted	Toddlers with ASD show preferential attention to biological motion, compared to TD and DD controls.	Inverted presentation to disrupt biological motion perception and processed by different neural circuits in infants up to 8 months. Significant implications of genetic predispositions profoundly exacerbated by atypical experiences.
11	(Nakano et al., 2010)	4:11 Y	3:1 Y	*N* = 25, 21 M	*N* = 25, 14 M	12 short A/V clips	Fixation time: eye, mouth, face, mouth/face	TD participants displayed highly stereotyped gaze patterns, compared to ASD variety in patterns: (1) shorter fixation time on the face; (2) preference for letter.	Study investigated temporal and spatial gaze patterns of children with and without ASD, while viewing ecologically relevant stimuli. Quantitative demonstration of TD subjects exhibiting highly stereotypical gaze patterns, while ASD subjects exhibit atypical gaze patterns.
12	(Norbury et al., 2009)	ALI: 14.9 Y ALN: 14.9 Y	TD: 14.50	*N* = 28, 27 M	*N* = 18 M	Digitized color video clips: story containing social interaction and emotional responses	Fixation time: Eyes Mouth Body Other	Children with ASD-LN showed: (1) profoundly less time fixating on eyes and (2) fixate slower on mouth, compared to TD. There was no difference in the viewing behavior patterns between ASD-LI and TD controls.	Differences in (1) viewing behavior associated with variations in language competence; and (2) fixation duration to the eyes, not likely to alter social abilities in daily interactions. Increased fixations to the mouth linked to greater communicative abilities across the spectrum.

(*Continued*)

TABLE 1
(Continued)

N	Authors	Mean age		Gender (M)		Stimuli type	Measures	Principal findings	Interpretation
		ASD	C	ASD	C				
13	(Noris et al., 2011)	5.3 Y	3.3 Y	N = 12, 11 M	N = 12, 11 M	Semi-structured live interaction with items, e.g., soap bubbles blowing, toy playing (WearCamera)	Vertical and lateral gaze angles	Children with ASD: (1) looked down more often (downcast) and (2) explored lateral field of view more extensively compared to TD children.	"Downcast" phenomenon in ASD reflects hypersensitivity to these stimuli. By down casting, children are more likely to view static stimuli that will not perturb them. Study favors theory of Enhanced Perceptual Functioning (arguing high frequency visual stimuli sensitivity in ASD).
14	(Noris et al., 2012)	5.3 Y	2.4 Y	N = 10, 9 M	N = 10	Naturalistic images (WearCamera)	Fixation time and number: vertical and lateral field of view	Compared to TD, children with ASD showed: (1) significantly less looking at face and for shorter amount of time; (2) when viewing more generally at environment, directed gaze further down (downcast gaze) and explored lateral field of view more extensively; and (3) preference for local features and less affection by perturbations of images (i.e., scene inversion).	Study identified generalized strategy of lateral gaze in ASD group while viewing objects. Downcast gaze to reflect sensory overload due to visual stimuli hypersensitivity, interpreted as an inability to filter excessive/ irrelevant information and distorted perception that generates anxiety, confusion and stress. Preference for local features to reflect why children with ASD use lateral field of view, given their need to examine more directly local features of objects and environment, compared to TD controls.
15	(Rice, Moriuchi, Jones, & Klin, 2012)	10 Y	9.5 Y	N = 37, 30 M	N = 26, 18 M	Free-viewing of dynamic social scenes in naturalistic contexts.	Fixation time: eyes, mouth, body, object	TD and ASD subjects: profoundly different visual fixation times on all ROIs (eyes, mouth, body and object) ASD focused: (1) less on eyes and mouth than controls and; (2) more on body and object; and (3) less viewing time focused on faces (eyes and mouth), relative to TD.	Profoundly altered social visual engagement patterns in children with ASD, with varying social adaptivity of behavior patterns within different groups. Strongest predictor of group membership: level of fixation on face area (eyes and mouth). Variability in these primal socialization mechanisms may indicate proximal behavioral manifestations of genetic vulnerabilities.

16	(Shic et al., 2011)	20.7 M	19.6 M DD: 19.3 M	*N* = 28, 20 M	*N* = 34, 22 M DD: *N* = 16, 10 M	30 s video of female adult and male toddler playing with puzzle	Fixation time: activity, background, people, head body	ASD children, compared to TD controls, exhibited; (1) atypical gaze patterns; (2) less interested and attentive to social stimuli (faces and social context); (3) viewed faces less frequently throughout a scene; and (4) shifted their gaze out of scene context, while TD naturally shifted gaze from one speaker to another and fixated on speaker until end of speech (eyes and mouth).	Eyes provide abundant information on emotion, identity and social phenomena, children viewed: (1) eyes, to collect social and emotional info; (2) mouth, to collect visual info related to speech Significantly increased mouth viewing and lack of efficient shift b/w eyes and mouth, may be an explanation for gaze patterns difference in two groups. Limited time spent at eye region while viewing speech communication, may lead to less social and emotional information being obtained from eyes, implicating future generation of misunderstandings and poor social communication skills.
17	(Speer, Cook, Mcmahon, & Clark, 2007)	13.6 Y	13.3 Y	*N* = 12 M	*N* = 12 M	20 digitized stimuli in four conditions: (1) social dynamic; (2) social static (3) isolated dynamic; and (4) isolated static	Fixation time: eyes, mouth, face/other, body, object. off	Compared to TD controls, ASD subjects, in social dynamic condition: (1) significantly less time viewing eyes; (2) marginally more time viewing body; and (3) decreased fixation duration for eye regions and increased for body regions.	Fixation duration in ASD group predicted scores on a measure of social responsiveness. ASD-associated deficits in face processing related to more general deficits in social functioning. Implications for early intervention treatment in increasing children's social responsiveness by training them to direct eye gaze more towards eyes, rather than body, during social interactions.

(*Continued*)

TABLE 1
(Continued)

N	Authors	Mean age		Gender (M)		Stimuli type	Measures	Principal findings	Interpretation
		ASD	C	ASD	C				
18	(van der Geest, Kemner, Camfferman, et al., 2002)	10.6 Y	9.9 Y	*N* = 16	*N* = 14	Cartoon like images with a human figure (2 blocks: 12 and 13 stimuli)	Fixation time and number human figure, another item	All children looked longer and more often towards human figure, compared to neutral objects.	No evidence of a general processing abnormality in first paradigm. Limitations: (1) highly controlled lab situation: implications of not being ecologically valid; and (2) social validity of full-color cartoon like images, of questionable quality.
19	(van der Geest, Kemner, Verbaten, et al., 2002)	(1)10.6Y (2) 10.8 Y	(1)10, 1 Y (2) 9.9 Y	(2) *N* = 16 M	(1) *N* = 16 M (2) *N* = 13 M	Study 1: Photos of human faces: (1) emotional; and (2) neutral expression, Study 2: Orientation (faces presented upside down)	Fixation time and number: face, mouth, eyes, eyes and mouth, other parts	ASD children: same fixation behavior as TD for upright faces, with/without emotional expression. TD controls: less time looking at upside-down faces, but fixation times of ASD children were not influenced by the orientation of the faces.	Abnormal gaze behavior in everyday life, not due to the presence of facial stimuli per se. Absence of a face orientation effect in ASD children likely to reflect lack of holistic processing of human faces in ASD.
20	(Wilson, Brock, & Palermo, 2010)	10.13 Y	10.65 Y	*N* = 13, 9 M	*N* = 14, 6 M	20 photos of natural scenes Passive viewing of five scenes	Fixation time and number: people, objects	Compared to TD controls, ASD exhibited: (1) similar tendency to fixate on people prior to objects but were slower to do so; (2) less time viewing peoples' faces; and (3) overall initial preference for attending to people, but their total looking time at people was reduced.	In ASD group, an individual's viewing preference first at people in scenes was associated with level of face recognition. Future research to determine existence of possible causal relationship between the two factors.

Abbreviations: ALI = autism language impaired, ALN = autism language not impaired, DD = developmentally delayed, TD = typically developing, SLI = specific language impairments, HR-ASD = high-risk ASD, AR-ASD = average risk ASD, L-R = low risk typically developing Sib = siblings, A/V = audiovisual, M = months/male, Y = years, ROI = region of interest.

without emotional expression. Both groups extended duration of fixation when looking at eye and mouth regions compared with other parts of the face (van der Geest, Kemner, Verbaten, et al., 2002). However, the second study showed that while neurotypically developing children diminished their fixation duration toward faces that were projected upside down, children with ASD exhibited similar fixation duration for both upside up and upside down faces, revealing less sensitivity to orientation of faces (van der Geest, Kemner, Verbaten, et al., 2002). Absence of a face orientation effect in children with ASD was suggested to reflect a compromised holistic processing mechanism of human faces in ASD. Adopting a similar approach but replacing photos of humans with cartoon-like images of human figures, van der Geest, Kemner, Camfferman, et al. (2002) reported the same duration as well as number of fixations toward human figures rather than objects, in both children with ASD and neurotypically developing controls. The findings do not support the notion that children with ASD exhibit atypical processing of socially visual stimuli and neutral objects. The experimental design did not allow for refined gaze analysis but instead the setup on the whole reflected a highly controlled laboratory situation that may have impacted on the social relevance of the experimental stimuli. Although both aforementioned studies did differ significantly in the nature of stimuli employed, static photos (van der Geest, Kemner, Verbaten, et al., 2002) versus cartoon-like images (van der Geest, Kemner, Camfferman, et al., 2002) of humans both yielded similar patterns of results. A conclusion that could be drawn at this point is that both types of visual representation of humans may be insufficient in encompassing an everyday social interaction, thus potentially impacting the ecological validity of the experimental paradigms employed.

Expanding on these study designs, Dalton et al. (2005) also conducted two studies investigating gaze fixation behavior, extending to the neural circuitry of face processing in ASD. The aim of both studies was to investigate the association between diminished duration of gaze fixation and neurophysiological abnormalities, employing eye tracking while measuring functional brain activity during face discrimination tasks. Similarly to van der Geest, Kemner, Verbaten, et al. (2002), in the first study they used emotional and neutral faces extracted from the Karolinska Directed Emotional Faces (KDEF) set. In the second study, they employed a facial recognition task to investigate the familiarity of a photograph. In both studies, compared to neurotypical controls, children with ASD (1) exhibited FG activation significantly and positively correlated with their duration of gaze fixation to the eyes region; and (2) varied their gaze fixation behavior, spending significantly diminished duration of fixation on the eyes as reflected by their amygdala activation, while there was no significant difference in the duration of fixation toward the mouth or face. Accordingly, the authors reported that while the former may suggest that compromised fixation duration may be the outcome of FG hypoactivation in response to faces, variation of their gaze fixation is also very likely associated with amygdala activation, hence highlighting a heightened emotional response commonly reported in ASD (Dalton et al., 2005). Notably, the study findings propose a model of atypical face processing in ASD, whereby deficits occur by hyperactivation in the central circuitry of emotion generate heightened sensitivity to social stimuli that in turn lead to compromised gaze fixation, resulting in atypical activation of FG. The same KDEF stimuli were also employed by Chawarska and Shic (2009) to examine visual scanning and face recognition in toddlers with ASD compared with controls. The study reported that compared with controls the toddlers with ASD atypically attended to key face regions and dwelled more on external rather than internal facial features, thus indicating impaired face recognition (Chawarska & Shic, 2009). In this study, recognition deficits were linked to imbalanced attention among key face regions.

A further study utilized static color photographs that included children faces, animal faces, toys, and landscapes to investigate visual scanning and pupillary responses as potential early markers in children with ASD (Anderson et al., 2006). Inconsistent with previous study findings (Adrien et al., 1993; Dawson et al., 2004; Klin et al., 2002; Osterling & Dawson, 1994; Pelphrey et al., 2002; Swettenham et al., 1998), this study did not provide evidence of classification of three groups characterized by their visual scanning of face stimuli. Again, as discussed for the studies of van der Geest, Kemner, Camfferman, et al. (2002) and van der Geest, Kemner, Verbaten, et al. (2002) inconsistency as such may lie in the nature of the stimuli employed; this study employed static as opposed to dynamic and multimodal stimuli. However, pupillary responses to face stimuli and duration of eye gaze fixation to landscape stimuli were the most robust predictors of group classification. Compared with neurotypical controls and developmentally delayed (DD) controls who both exhibited pupillary dilation, children with ASD exhibited pupillary constriction while increasing duration of their gaze toward landscape photographs (Anderson et al., 2006). Low sample

size did not allow the study to determine measures that differentiate ASD groups from neurotypically developing groups. Similar to Anderson et al. (2006), Key and Stone (2012) presented three color pictures of human faces (standard face, same face but different eyes, same face but different mouth) to infants at average and high risk of ASD, with the objective to investigate whether an increased risk of ASD was linked to a difference in processing of facial features (i.e., eyes compared to mouth). The results indicated that both groups had similar gaze patterns; they increased fixation duration toward faces and facial features compared to hair, body, and background elements and exhibited similar number and duration of fixation toward eyes and mouth regions (Key & Stone, 2012). Consequently, there were no significant group differences in face-viewing patterns, corroborating previous findings while suggesting (i) 12–24 months as the onset of atypical behavior in ASD symptomatology, that is, failure to respond to name calling (Key & Stone, 2012; Nadig et al., 2007; Zwaigenbaum et al., 2005); and (ii) lack of ecological validity indicated by the nature of static photos of human faces (Anderson et al., 2006; van der Geest, Kemner, Camfferman, et al., 2002; van der Geest, Kemner, Verbaten, et al., 2002). A separate study investigating gaze fixation correlated with brain activation and amygdala volume, extended the investigation of atypical patterns and brain behaviors, to unaffected siblings of children with ASD (Dalton et al., 2007). In response to naturalistic photos of un/familiar human faces, both ASD and sibling groups (1) diminished their fixation duration toward the eye region and (2) exhibited hypoactivation in the right FG, as compared with controls. Extending to Dalton et al. (2005), this study provided evidence for different social/emotional processing and underpinning neural circuitry in first-degree relatives of children with ASD. Wilson et al. (2010) edited 20 photographs of natural scenes so that each one would include people and objects (i.e., van, ice-cream, pelican) and presented them to children with ASD and controls. Their aim was to record eye gaze pattern behavior while both groups were passively viewing and to identify a possible correlation between compromised face recognition and reduced attention toward social stimuli in ASD as proposed by Schultz (2005). Replicating previous studies, neurotypically developing children preferentially attended to social prior to nonsocial stimuli in scenes. A similar tendency was exhibited by children with ASD; however, the speed of orienting their gaze toward social stimuli was significantly slower, relative to controls. Further to this, while duration of fixation for controls was longer for social stimuli, children with ASD exhibited equal duration of fixation for both social and nonsocial stimuli, and a diminished duration for faces in particular (Wilson et al., 2010). Adding to this, a brief report in 2011, by Bradshaw and colleagues, extended the traditional visual experimental paradigms to study memory deficits by utilizing a visual paired comparison paradigm comprised color pictures (neutral faces, objects, and block patterns). The study aim was to ascertain whether recognition impairments in children with ASD were targeted toward faces or whether it is part of a generalized impairment in processing extending to nonsocial stimuli (Bradshaw et al., 2011). The study confirmed previous findings in regards to specific impairments in face encoding and recognition (Chawarska & Shic, 2009; Klin et al., 1999). Further, it replicated a targeted advantage to nonsocial stimuli as demonstrated by their performance in block design tasks and characterized by a "weak central coherence" model, highlighting a detail-focused style of processing nonsocial stimuli (Happé & Frith, 2006; Rinehart, Bradshaw, Moss, Brereton, & Tonge, 2000; Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008). In conclusion, as previously highlighted by Dalton et al. (2005, 2007), the authors suggested that these impairments extend beyond attention, highlighting underlying deficits in the neural mechanism of processing relevant stimuli.

Moving from static photographs (static stimuli) to interactive experimental paradigms, several research groups have employed audiovisual stimuli in their eye-tracking studies in children with ASD. This category of studies is more complex in its implementation in young children; however, it is considered to stand out in ecological relevance compared to still photographs. Speer et al. (2007) utilized 20 digitized stimuli to measure preferential viewing across the eye, mouth, face, or other body regions or objects. Stimuli were presented in four conditions: (1) social dynamic, (2) social static, (3) isolated dynamic, and (4) isolated static. The most interesting finding arose from the social dynamic condition. That is, relative to controls, individuals with ASD significantly reduced their duration of fixation to the eye region and increased duration to the body (Speer et al., 2007). Specifically, diminished fixation duration to the eyes was correlated with an increased fixation duration pattern to the body, further predicting scores on a measure of social responsiveness (Speer et al., 2007).

In a similar idea, Jones et al. (2008) employed audiovisual stimuli to quantify preferential viewing, across regions of the eyes, mouth, body, and objects, in 2-year-old toddlers with ASD. Compared to neurotypical controls and DD toddlers, toddlers with ASD

exhibited significantly decreased visual fixation duration on the eye region and simultaneously increased their fixation duration on the mouth region (Jones et al., 2008). In addition, reduced fixation duration on the eyes predicted greater level of social disability (Jones et al., 2008). Most importantly, it highlighted the significance of understanding ontogenetic mechanisms in ASD. That is, while neurotypical controls exhibited stereotypical eye gaze fixation and appropriate duration patterns, children with ASD aberrant gaze patterns indicate divergence from a neurotypical process of socialization that namely lies in (1) spontaneous searching for eyes and (2) responding to gaze cues that infer mental states (Jones et al., 2008; von dem Hagen, Stoyanova, Rowe, Baron-Cohen, & Calder, 2013). As a result, this divergence has been suggested to not only impact language acquisition but also shape an atypical mind and brain (Johnson, 2001; Klin, Jones, Schultz, & Volkmar, 2003). Extending to the previous study designs, digitized color video clips including a story with a social interaction and emotional responses were also employed to measure fixation duration on the eyes, mouth, body, and other regions (Norbury et al., 2009). Study participants involved ASD children with language skills that were deemed to be normal (i.e., autism language normal (ALN)) or impaired (i.e., autism language impaired (ALI)). Compared to controls, children with ALN exhibited significantly diminished duration of fixation to the eyes. Surprisingly, no difference was detected in the duration of fixation to the eyes between ALI and TD groups, demonstrating for the first time typical fixation patterns in ASD in the context of dynamic social stimuli viewing (Norbury et al., 2009). This between-group variation was suggested to reflect underlying cognitive and/or perceptual differences, such as level of ocular motor control abilities. Additionally, increased fixations to the mouth were associated with variation in language acquisition and greater communicative competence in children with ASD (Norbury et al., 2009). Stimuli from audiovisual clips were also employed by Nakano et al. (2010) to investigate both temporal and spatial eye gaze patterns. Aligned with previous findings in nonsocial compared to social stimuli (Klin et al., 2002), this study reported that while control children revealed stereotypical gaze patterns, children with ASD exhibited (1) shorter fixation duration when facial stimuli were presented, as well as (2) a preference to viewing letters rather than social stimuli (Nakano et al., 2010). Notably, eye-mouth fixation proportions were not a discrimination marker between ASD and control groups.

Employing a video task that depicted an adult and child during play a further study investigated monitoring preferences of toddlers with ASD, neurotypical, and DD controls (Shic et al., 2011). Compared to both control groups, the duration of fixation for ASD toddlers was shorter toward subjects' activities, specifically shorter at the head region, while longer at the body region of social stimuli and nonsocial stimuli in the background (i.e., toys) (Shic et al., 2011). These findings suggest that from an early developmental stage (i.e., 20 months), the ability of children with ASD to monitor social activities is compromised and may therefore underlie progressive impairments in later developmental stages (Shic et al., 2011). Although knowledge regarding early onset of such impairments is not yet sufficient, a recent prospective longitudinal study in infants later diagnosed with ASD showed compromised eye fixation patterns at 2–6 months of age. Interestingly, these patterns were not observed in typically developing infants (Jones & Klin, 2013). This marked indicator of social impairment in ASD highlights the process of decline, revealing the earliest onset known thus far. A similar experimental paradigm to Shic et al. (2011) was used to measure visual fixation during free viewing in older children. In all regions of interest (i.e., eyes, mouth, body, and objects), ASD children showed profoundly different visual fixation orienting their gaze away from socially salient aspects of the scenes compared to neurotypical controls (Rice et al., 2012). Most significantly, children with ASD reduced their fixation duration to eyes compared to mouth regions (Rice et al., 2012). Once again, level of fixation on either the eyes or mouth predicted the subject's membership in either one of the groups (Rice et al., 2012). In this study, although patterns of social engagement via visual stimuli were shown to be severely atypical in children with ASD, there was significant variation in the patterns within-group populations. In order to ascertain whether this variation is associated with a genetic predisposition or compensatory learning, both adaptation and maladaptation require future follow-up across the child's primal years to Rice et al. (2012). Adding to the existing literature, a study directed on deficits in language acquisition reported atypical gaze patterns for the children with ASD, accompanied by diminished interest and attendance to social stimuli throughout a scene, compared to the controls (Hosozawa et al., 2012). Specifically, control children shifted their eye gaze (toward both eyes and mouth) naturally from one speaker to the other during speech communication while children with ASD shifted their eye gaze out of the context of the scene (Hosozawa et al., 2012). These findings were consistent with previous findings in children with ASD reporting compromised social skills with profound implications

to the collection of information from the eyes and mouth, which ultimately lead to poor social communication and deficits in understanding (Hosozawa et al., 2012).

A recent study on 6-month-old infants that were later diagnosed with ASD utilized a free-viewing task with the aim to detect spontaneous regulation of attention and response to multimodal stimuli in four conditions of motion (Chawarska et al., 2013). The study used four groups: children with ASD, high-risk atypically developing (HR-AD), high-risk typically developing (HR-TD) and low-risk/no history of ASD (LR-TD). Six-month-old infants later diagnosed with ASD showed compromised attention to social scenes and in cases that they did attend, their duration of fixation was shorter toward social stimuli in general and specifically the face (Chawarska et al., 2013). Interestingly, atypical pattern directed to social stimuli (i.e., subject or a subject's face regions) was not accompanied by increased duration of fixation toward nonsocial stimuli (objects) (Chawarska et al., 2013). The study raised the issue of continuity in ASD in both social attention impairments per se and the evolution of the impairments in the sphere of interaction and communication (Chawarska et al., 2013). Importantly, this was the first study to demonstrate prodromal behavioral patterns in ASD at 6 months, thus highlighting that it may be possible to identify visual phenotypic behaviors and use these as diagnostic tools in ASD in first year of life (Chawarska et al., 2013). These uncharacteristic gaze behavior patterns in ASD were later replicated in infants 2–6 months of age, providing new insight on the onset symptomatology in ASD (Jones & Klin, 2013).

The first attempt to investigate biological motion perception in ASD aimed to investigate the manner in which 2-year-old children relate to and facilitate adaptive interaction with others at this early stage of brain development, hallmarked by the absence of any compensatory coping strategies (Klin et al., 2009). A preferential attention paradigm of point light displays of biological motion accompanied by audiovisual matching the motion/action was employed to examine orientation to nonsocial, physical contingencies, compared to other biological motion displays (Klin et al., 2009). This study paradigm contained figures on a split screen, in two conditions: (1) standard upright with audiovisual of vocalizations and (2) inverted played in reverse order (no audiovisual). Increased fixation toward the upright condition (accompanied by matching of human voice) provided evidence for recognition and preferential attention to biological motion. Inverted condition was introduced as a bias toward biological motion perception, which is processed by different neural circuits in infants up to 8 months of age (Klin et al., 2009). Compared to neurotypical and DD controls whose attention was directed to biological motion, children with ASD failed to orient to such motion exhibiting random patterns of visual scanning, relative to social content. Further, for the between-group analysis, the ASD group showed significant preference for the upright condition in instances where the animation task included a physical contingency (a condition where human interaction takes place) as opposed to animations without physical contingencies. Interestingly, as revealed by post hoc quantification of audiovisual synchronies (AVS) and preferential looking, 90% of reported atypical viewing behavior in 2-year-old children with ASD, reflected a marked reliance on AVS (Klin et al., 2009). Such reliance was not evident in either neurotypically developing nor DD controls (Klin et al., 2009). In support of naturalistic techniques, another research group sought to extend eye-tracking studies on children with ASD by utilizing a "WearCamera"; an eye tracker, worn by the children (Noris et al., 2011). During a semi-structured interaction with a variety of items, this study investigated eye gaze from the child's viewpoint (Noris et al., 2011). Relative to controls, children with ASD were reported to exhibit the "downcast" phenomenon, in that they looked down, more often (Noris et al., 2011). Moreover, they also were found to explore the lateral field of view in more detail compared to controls (Noris et al., 2011). The implication for the "downcast" phenomenon was that by looking downward children with ASD were better able to view static elements (i.e., objects like a table, and also the ground itself) and it was posited that these static elements were less likely to create any form of agitation or emotional stress to the ASD children (Noris et al., 2011). In this study, the vast majority of the visual stimuli were present on the top part of the screen leading the authors to suggest that the "downcast" phenomenon reflects their hypersensitivity to these stimuli (Noris et al., 2011). This sensitivity to high-frequency visual stimuli has been previously described in the theory of enhanced perceptual functioning (Mottron, Dawson, Soulières, Hubert, & Burack, 2006). The same naturalistic effect (WearCamera) was utilized in the same year, with a slight variation in the stimuli presented to children. The same authors set out to investigate the eye gaze strategies of children with ASD and controls while viewing naturalistic images (Noris et al., 2012). Consistent with the previous literature (Noris et al., 2011), study findings reported that children with ASD exhibited aberrant eye gaze toward faces as indicated

by shorter duration of fixation on salient face regions compared to controls. Once again, "downcast" gaze reflected a sensory overarousal triggered by visual stimuli, especially when subjects were viewing the broader environment.

META-ANALYSES

Methods

In the meta-analyses, studies were included only if they provided sufficient data to determine the effect size of the study or if we were able to obtain these values from the authors via correspondence. We conducted two such analyses: eight studies were included for the eye-fixation duration meta-analysis and six for the mouth-fixation duration meta-analysis. Two articles incorporated two separate studies (experimental paradigms) each, on different populations; hence, both studies were included in the two meta-analyses (Dalton et al., 2007; Jones et al., 2008). On this note, each study provided separately eyes and mouth fixation data and as such, these observations were treated separately in the two meta-analyses. As summarized in Figure 1, the first meta-analysis reported eye-fixation duration results from Studies I and II conducted by Dalton and colleagues (i.e., "Dalton et al., 2005 (I) E": n = 14 males with ASD, ASD mean age = 15.9 years, "Dalton et al., 2005 (II) E": n = 16 males with ASD, ASD mean age = 14.5 years) (2005) and Studies I and II by van der Geest and colleagues (i.e., "van der Geest, Kemner, Verbaten, et al., 2002 (I) E": n = 17 males with ASD, ASD mean age = 10.6 years, "van der Geest, Kemner, Verbaten, et al., 2002 (II) E": n = 16 males with ASD, ASD mean age = 10.8 years). Similarly, as summarized in Figure 2, the second meta-analysis reported mouth-fixation duration results from Studies I and II conducted by van der Geest and colleagues ("2002 (I) M": n = 17 with ASD, ASD mean age = 10.6 years. "van der Geest, Kemner, Verbaten, et al., 2002 (II) M": n = 16 with ASD, ASD mean age = 10.8 years). In Study II, only the "upright in orientation" condition was included in the analyses. One study (Jones et al., 2008) included in the analyses provided fixation duration data in four conditions (social dynamic, social static, isolated dynamic,

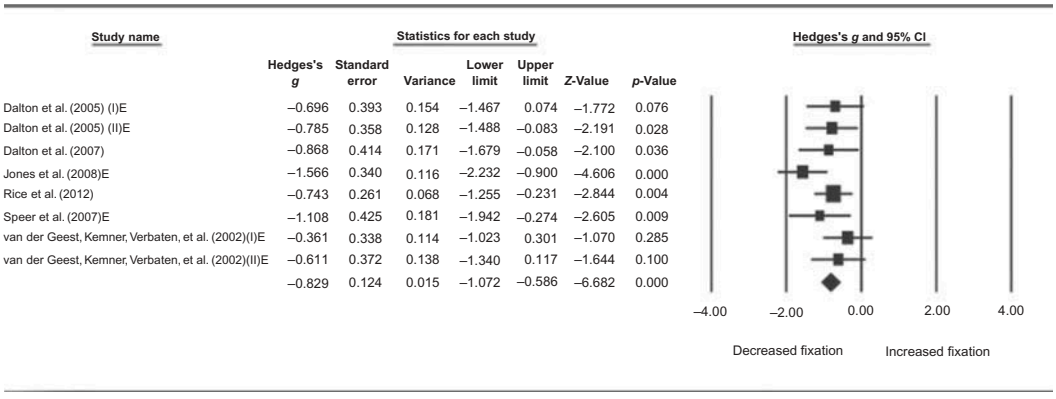

Figure 1. Forest plot of eye gaze fixation directed toward the eye region in children with ASD and their 95% confidence intervals.

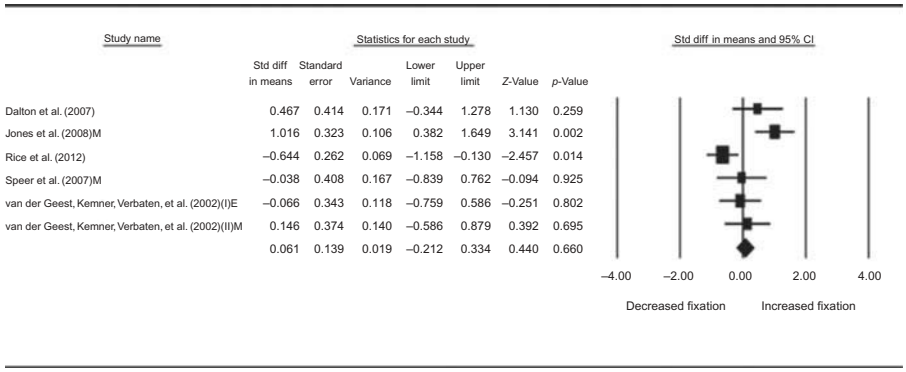

Figure 2. Forest plot of eye gaze fixation directed toward the mouth region in children with ASD and their 95% confidence intervals.

isolated static) of which only social dynamic data were included. Following our request for unpublished (mouth and eyes) duration fixation data, an additional study was included (Speer et al., 2007).

In total, the eye-fixation meta-analysis included eight studies (Dalton et al., 2007, 2005; Jones et al., 2008; Rice et al., 2012; Speer et al., 2007; van der Geest, Kemner, Verbaten, et al., 2002) and the mouth-fixation meta-analysis included six studies (Dalton et al., 2007; Jones et al., 2008; Rice et al., 2012; Speer et al., 2007; van der Geest, Kemner, Verbaten, et al., 2002). Study populations included children with ASD compared to control groups.

Procedure

Meta-analyses were conducted using comprehensive meta-analysis developed by Biostat (Borenstein, Hedges, Higgins, & Rothstein, 2005). Effect sizes were standardized mean differences in duration of fixation on the (1) eye region and (2) mouth region. Standardized mean differences were reported with *Hedges'* correction for small samples using 95% confidence intervals. Hedges' effect size (g) was interpreted in the same way as Cohen's d: 0.2 = small; 0.5 = medium; and 0.8 = large (Cohen, 1988). Alpha was set to 0.05. The Q-statistic was reported to index significant heterogeneity of effect sizes across studies, and I^2 was the effect size quantifying this heterogeneity. An I^2 of 0.25, 0.50, and 0.75 denoted small, moderate, and high levels of heterogeneity, respectively (Higgins & Thompson, 2002). Alpha was set to 0.10 to test for heterogeneity as this procedure typically lacks power (Higgins, Thompson, Deeks, & Altman, 2003). Random effects modeling was adopted over fixed-effect modeling since the latter assumes there is no variation in effects across studies over and above sampling error. Random modeling provides a more conservative estimate of the pooled effect size and therefore less likely to inflate the true effect. Publication bias was assessed using Eggers' test (Egger, Smith, Schneider, & Minder, 1997).

RESULTS

Eye fixation

Overall there was a significant effect size between duration of fixation on the eyes in the ASD population compared to controls (Hedges' g = 0.831, 95% CI: −1.66 to −0.575, $p < 0.001$). The effect sizes for each study are shown in Figure 1. Heterogeneity of effect sizes was not significant ($x^2 = 7.635$, $I^2 = 8.321$, $p > 0.1$) and similarly the Eggers' test was not significant ($p > 0.05$).

Mouth fixation

Overall there was a nonsignificant effect size for duration of fixation to the mouth region in the ASD population compared to neurotypical controls (Hedges' g = 0.123, 95% CI: −0.380–0.627, $p > 0.05$). However, the heterogeneity of effect sizes was significant across the studies ($x^2 = 17.208$, $I^2 = 70.944$, $p < 0.1$) and thus the robustness of these findings needs to be interpreted with caution. Finally, the Eggers' test was not significant ($p > 0.05$). The effect sizes for each study are plotted in Figure 2.

DISCUSSION

Aberrant patterns of eye gaze and fixation times have been reported by numerous ASD studies and indeed several have proposed that eye gaze abnormalities are a biomarker of the condition that can be utilized for early detection and diagnosis (Boraston & Blakemore, 2007). However, while the ASD eye gaze literature is expanding, as yet there does not appear to be a convergence of findings. The heterogeneous nature of the condition almost certainly assumes a significant role, but the variability in findings across studies may also be due, in part, to the variety of experimental paradigms and technologies that have been employed. In our meta-analyses, we sought to evaluate two eye gaze abnormalities that have previously been reported in ASD: (1) *atypical* gaze *directed to* the eyes of the human face and (2) *atypical* gaze *to* the mouth of the human face. Meta-analyses of the identified studies revealed that patterns of eye movements directed toward the eyes were significantly abnormal in children with ASD. However, no significant effect was found for the patterns of eye movements that involved looking at the mouth. It should be noted that the lack of any significant difference for mouth fixation however needs to be cautiously interpreted since the findings might be influenced by a lack of statistical power (N = 6 studies in the mouth meta-analysis) and high heterogeneity.

The meta-analysis findings for eye fixation revealed that compared to neurotypical controls, children with ASD exhibit significantly reduced gaze fixation on the eyes when viewing human faces. Notably, the effect size for this variable was large (Hedges' g = 0.831) and overall statistically

significant. The strength of this result is of particular importance as it offers the possibility that aberrations in the fixation to the eyes may be of diagnostic relevance. This result lends credence to those early intervention programs specifically implementing eye gaze interventions and furthermore corroborates the findings of previous studies that have suggested this impairment represents a reduced holistic processing strategy that is characteristic of the severity of the disorder. Moreover, it has been posited that atypical gaze patterns in the eye region also represents a critical quantitative behavioral and phenotypic trait of ASD (Boraston & Blakemore, 2007).

Diminished attention to the eyes during social interactions has significant implications across multiple domains of a child's development. These include negatively impacting communication (Norbury et al., 2009), social interactions (Bradshaw et al., 2011), theory of mind (von dem Hagen et al., 2013), as well as language development (Hosozawa et al., 2012; Norbury et al., 2009). Indeed, failure to observe or understand important communication cues leads to the misattribution t of social cues (e.g., gaze, shifting head toward speaker, the significance of cheering at a social event and social smiling), which ultimately results in the failure to develop theory of mind in these children (von dem Hagen et al., 2013; Zwaigenbaum et al., 2005). Absence or the underdevelopment of capacities, such as theory of mind, directly disrupts the ability to follow verbal instructions in real-life situations and/or within academic environments. Most often this promotes a sense of constant underachievement and diversity (compared to peers/colleagues), leading to gradual isolation patterns. Alternatively, in instances where the individual is quite enthusiastic, verbal and extroverted, the preferential avoidance of others' eyes can result in the failure to detect more complex emotional states such as sarcasm as well as the possible lack of interest. In such instances, individuals with ASD can dominate a discussion, which may have no value from the audience's point of view and as a consequence cause social disengagement and lead to isolation patterns.

The meta-analysis findings for mouth fixation revealed that compared to controls, children with ASD show no significant differences in fixating to the mouth when exposed to faces of humans. The robustness of this finding is uncertain given the high heterogeneity of the mouth fixation data; however, with these caveats in mind, this result is in contrast with a number of previous studies (Jones et al., 2008; Klin et al., 2002; Norbury et al., 2009; Rice et al., 2012). Previous studies have suggested that fixating on the mouth serves as a compensatory strategy the aim of which is to retrieve information and social cues lost through reduced attention to the eyes. However, this trend has not been consistently reported in the literature and may be reflected in the results of our meta-analysis. It has been established that neurotypically developing infants (18–20 weeks old) recognize correspondence between speech sounds presented in either auditory or visual way, and that the information conveyed by the sounds is significant to the detection of such correspondences (Kuhl & Meltzoff, 1982). Hence, given this bimodal perception (auditory and visual) in speech acquisition, toddlers learning to speak would be expected to exhibit some fixation on the mouth (Kuhl & Meltzoff, 1982). The results of our meta-analysis support this conceptualization, although we do acknowledge that discrepancy in stage of language acquisition and, furthermore, the age and developmental stage of an individual with ASD, may explain the level of increased fixation to the mouth. That is, older and average to highly verbal/social individuals with ASD may seek communicative cues (mouth serving as a tool for language) more, compared to nonverbal, younger individuals.

Another interesting theoretical speculation was discussed by Jones et al. (2008) according to which, in studies where alongside visual non/social stimuli, ADV effects are also incorporated in the background, increased mouth fixation patterns may be prompted and attributed to the synchrony of the ADV per se. This purports an alternative learning path for language, where language skills are being acquired with the help of physical features (motion/sound) rather than social-affective features (speech sounds as social cues) (Jones et al., 2008). Finally, most recently presented data by Evers, Hermens, Steyaert, Noens, and Wagemans (2013) on global scanning patterns in children with and without ASD while watching video clips have revealed no differences in the number and duration of fixation, or saccade amplitude, between these two groups. Preliminary analysis has also shown no differences in viewing time, when fixation patterns were compared on four dynamic areas of interest that include the mouth (Evers et al., 2013), Despite the absence of marked differences in fixation patterns, compared to the neurotypically developing group, the ASD group tended to perform worse on social emotional questions that followed the video clips. As expected, this tendency was mostly evident in questions involving emotion recognition and emotion clarification. Conversely, the ASD group performance was enhanced when questions involved visual details (Evers et al., 2013). Similar findings were also shown in a facial emotion recognition and visual search task, where no difference was found between children with

high functioning ASD/Asperger's syndrome and neurotypically developing children for either total number of fixations or emotional ability (Leung, Ordqvist, Falkmer, Parsons, & Falkmer, 2013). Also, although both groups fixated more toward the eyes, fixation duration was longer in children with ASD, indicating different task demands.

Notably, this trend marked by the absence of different viewing patterns in children with ASD, while they still perform poorly or intact on emotion recognition tasks, brings new insight in the field, implicating the validity and reliability of eye-tracking techniques as a measure of aberrant social behavior in ASD. This raises a point for future consideration; if eye gaze orienting is intact, but processing of information is impaired, then perhaps there is an imperative to move focus from eye gaze behavior to the underpinning neural circuitry responsible for impairments in ASD. While in the present meta-analysis we did not find a significant effect for eye gaze fixation to the mouth region, the literature suggests that there may be a more complex relationship between mouth fixation and emotional processing. For example, studies have shown that mouth fixation and face processing can be modulated by emotional state (Curby, Johnson, & Tyson, 2012). Perhaps this relatively new insight provides an avenue for future research where emotional state is incorporated into ASD eye gaze studies and may strengthen the overall reliability of findings.

LIMITATIONS AND FUTURE CONSIDERATIONS

There are a number of limitations inherent in studies of eye gaze, primarily associated with the absence of a distinct difference in viewing patterns (i.e., fixation on mouth region). While fixation duration on the mouth, for instance, may be intact, children with ASD still exhibit difficulties when presented with emotion recognition tasks and social interactions compared to controls. Hence, what is yet to be explicated is whether marked (viewing) patterns or the absence of these in face processing are correlated with the processing of information.

In terms of limitations, the mouth fixation studies warrant further discussion. In the analysis of these studies, a large heterogeneity of effect sizes was observed, which was most likely due to the limited number of studies that met the inclusion criteria. As such, it was not possible to conduct a meta-regression analysis; subsequently, the mouth fixation findings need to be interpreted cautiously. A further issue for future consideration is that of ecological validity. Highly controlled lab situations, cartoon-like social stimuli, emotional expressions presented in black and white still photographs, poorly encapsulate naturalistic environments. In fact, it has been proposed that unstructured settings are more likely to reveal impairments social cognition and processing in ASD (Klin et al., 2002). Next, it would be beneficial if study populations employed were larger in size and at the earliest possible stage of development. Alongside this, longitudinal follow-up could then extend the scope of research, investigating gaze behavior and patterns of fixation in the course of atypical development in ASD and look at the extent to which these impose on the development of social cognition, language competence, and social skills in real-life conditions. Equally important, combining functional imaging with eye-tracking studies may offer new insights into causal relationships with respect to whether aberrant eye gaze is centrally mediated or indeed it drives much of the observed impairments in cognition. The final issue lies in early intervention treatment aiming to improve social responsiveness. Computerized emotion and/or face-specific training have been designed to target atypical discrimination, recognition, and memory of faces, increasing familiarity and redirecting visual attention, in children and adolescents with ASD (Blair, Frith, Smith, Abell, & Cipolotti, 2002; Faja, Aylward, Bernier, & Dawson, 2007; Klin et al., 1999; Williams, Goldstein, & Minshew, 2005). To date, only a few studies have investigated the extent to which such training can positively impact face processing strategies (Baron-Cohen, Hill, Golan, & Wheelwright, 2002; Bölte et al., 2002; Silver & Oakes, 2001) and their efficacy is still being explored. Recent studies have placed significant limitations in the ecological validity of such training protocols aiming to develop emotion perception (Golan & Baron-Cohen, 2006; Silver & Oakes, 2001). For example, improvements in key domains on computerized tasks, individuals with ASD, failed to be extended to naturalistic conditions (Faja et al., 2007). However, some argue that this artificial nature of computerized training in fact encourages the development of unfamiliar face processing-related skills in individuals with underdeveloped capacities (Faja et al., 2007). In this regard, it is imperative to refine the design of programs that direct gaze behavior preferentially toward the eye regions in social interactions (Speer et al., 2007) and emphasize on emotion recognition (Boraston & Blakemore, 2007) to further explore improved performance on real-life events and/or in theory of mind measures (Silver & Oakes, 2001).

CONCLUSIONS

The findings of our meta-analyses indicate that children with ASD have significantly impairments in eye gaze fixation when viewing the eyes but not the mouth of human faces. These findings add clarity to an expanding literature and suggest that eye gaze fixation to the eye region may represent a biomarker, quantifying early syndrome manifestation specific to ASD. However, similar findings of face processing deficits and reduced fixations to the eye region in particular have also been reported in individuals with schizophrenia (Morris, Weickert, & Loughland, 2009) as well as conduct disorder (Dadds, El Masry, Wimalaweera, & Guastella, 2008). It is of considerable interest to delineate whether in the case of ASD impairments arise from the way individuals scan social and nonsocial stimuli, or rather the way that they process this social information. However, given the available evidence, at this point in time it is not possible to distinguish between these disorders on the basis of eye gaze behavior alone, as there is significant overlap in abnormal gaze characteristics across the disorders.

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