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Preterm birth is associated with atypical social orienting in infancy detected using eye tracking

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Background: Preterm birth is closely associated with neurocognitive impairment in childhood including increased risk for social difficulties. Eye tracking objectively assesses eye-gaze behaviour in response to visual stimuli, which permits inference about underlying cognitive processes. We tested the hypothesis that social orienting in infancy is altered by preterm birth. **Methods:** Fifty preterm infants with mean (range) gestational age (GA) at birth of 29⁺¹ (23⁺²–33⁺⁰) weeks and 50 term infants with mean (range) GA at birth 40⁺² (37⁺⁰–42⁺³) weeks underwent eye tracking at median age of 7 months. Infants were presented with three categories of social stimuli of increasing complexity. Time to first fixate (TFF) and looking time (LT) on areas of interest (Aois) were recorded using remote eye tracking. **Results:** Preterm infants consistently fixated for a shorter time on social content than term infants across all three tasks: face-scanning (fixation to eyes minus mouth 0.61s vs. 1.47s, $p = .013$); face pop-out task (fixation to face 0.8s vs. 1.34s, $p = .023$); and social preferential looking (1.16s vs. 1.5s $p = .02$). Time given to Aois containing social content as a proportion of LT at the whole stimulus was lower in preterm infants across all three tasks. These results were not explained by differences in overall looking time between the groups. **Conclusions:** Eye tracking provides early evidence of atypical cognition after preterm birth, and may be a useful tool for stratifying infants at risk of impairment for early interventions designed to improve outcome. **Keywords:** Social orienting; development; preterm infant; eye tracking.

Introduction

Globally, preterm birth [delivery at <37 weeks' gestational age (GA)] affects around 10% of deliveries (Blencowe et al., 2012) and is a leading cause of neurocognitive impairment and educational underperformance (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Delobel-Ayoub et al., 2009; MacKay, Smith, Dobbie, & Pell, 2010; Quigley et al., 2012). The preterm neurocognitive profile includes global and specific learning difficulties, executive dysfunction, inattentiveness, social difficulties and increased likelihood of screening positive for, or receiving a diagnosis of autism spectrum disorder (ASD; Johnson et al., 2010; Johnson & Marlow, 2011; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Guy et al., 2015). Identification in infancy of children with atypical development would enable targeting of early interventions designed to improve outcome, when they are likely to be most effective (Warren et al., 2011; Wass, Porayska-Pomsta, & Johnson, 2011; Koegel, Koegel, Ashbaugh, & Bradshaw, 2014).

Oculomotor orienting (gaze) behaviour is a critical control point for intake of visual information and its assessment in response to visual stimuli can be used to make inferences about underlying cognitive processes including preference, memory, attention and processing speed (Liversedge & Findlay, 2000; Fletcher-Watson, Findlay, Leekam, & Benson, 2008; Fletcher-Watson, Leekam, Benson, Frank, &

Findlay, 2009; Johnson, Senju, & Tomalski, 2015). In the developmental trajectory of social cognition visual attention is given to faces very soon after birth, with specific attention paid to the eye region; and later in infancy at around 6–9 months a preference for looking at faces within multiple object arrays or animated scenes develops (Johnson, Dziurawiec, Ellis, & Morton, 1991; Farroni, Csibra, Simion, & Johnson, 2002; Gliga, Elsabbagh, Andravizou, & Johnson, 2009; Frank, Vul, & Johnson, 2009); for review see (Johnson et al., 2015). This trajectory is altered from 2 to 12 months in children who go on to receive a diagnosis of ASD, which suggests that gaze behaviour may be one of the earliest markers of atypical social cognition (Young, Merin, Rogers, & Ozonoff, 2009; Ozonoff et al., 2010; Chawarska, Macari, & Shic, 2012; Jones & Klin, 2013; Chawarska, Macari, & Shic, 2013; Wass et al., 2015).

Eye-tracking provides a nonbiased assessment of gaze in response to visual stimuli that is highly resolved in time (milliseconds) and space, which enables calculation of time to first fixate (TFF) and looking time (LT) to predefined areas of interest (AoI). It is well suited to studying gaze behaviour during infancy because it can be applied to nonverbal populations and has high test-retest reliability for individual differences in this age group (Wass & Smith, 2014; Gillespie-Smith et al., 2015).

Based on studies of the developmental trajectory of social cognition and the clinical phenotype of children and adults born preterm, we hypothesised that preterm birth would be associated with alterations in

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cognition detectable during infancy. We used eye tracking to measure gaze behaviour because of its utility for assessing social phenotypes in this age group. We assessed children at a median of 7 months of age, and report differences in orienting to social cues between those born preterm compared with age-matched peers born after 37 weeks' gestation.

Methods

Participants

Preterm infants (GA at birth $<33^{+0}$ weeks) were recruited from the Royal Infirmary of Edinburgh, and healthy term control infants (≥ 37 weeks' GA) were recruited from the postnatal wards or community groups between February 2013 and April 2015. A subset of the control infants have been reported previously (Gillespie-Smith et al., 2015). The Scottish Index of Multiple Deprivation (SIMD) was used to characterise deprivation. The SIMD is the official Government tool used to identify areas of deprivation: it divides Scotland into around 6,505 areas each containing around 350 households and assigns an index to each area based on multiple measures of deprivation. The data are ranked from most to least deprived and are presented as quintiles. Exclusion criteria: major congenital malformations, chromosomal abnormalities, congenital infection and infants with major overt parenchymal lesions (cystic periventricular leukomalacia, haemorrhagic parenchymal infarction) and posthaemorrhagic ventricular dilatation. Ethical approval was obtained from the National Research Ethics Service (South East Scotland Research Ethics Committee 02) for all participants recruited from hospital services; ethical approval for the recruitment of community participants was granted by the School of Education Ethics Sub-Committee, University of Edinburgh. Informed written parental consent was obtained.

Eye-tracking assessment

Participants were invited for assessment at 6–10 months (corrected gestational age was used for the preterm group because this is the standard practice for neurodevelopmental assessment of children born at <32 weeks until the age of two years (Johnson & Marlow, 2006)). Infants were positioned on their caregiver's lap 50–60 cm from a display monitor used to show visual stimuli. Eye movements were detected using a Tobii[®] x60 eye-tracker and Tobii Studio[®] (version 3.1.0) software was used to present stimuli and record eye movements for analysis. Images were presented on a display monitor with a resolution of 1,440 × 900 pixels. The Tobii[®] x60 system tracks both eyes to a rated accuracy of 0.3 degrees at a rate of 60 Hz. Prior to data collection, eye-tracking calibration was performed using a five-point system. Preterm infants were screened for deficits in visual acuity (VA) using Keeler[®] acuity cards prior to eye tracking, and infants were excluded if VA was below the estimated norm for age (Speedwell, 2003).

Tasks

We presented three tasks of increasing complexity (Figure 1) that have been validated (Gliga et al., 2009; Gillespie-Smith et al., 2015). Each task contained different stimuli and these were presented in blocks with variable order. Attention grabbers (cartoon images of toys on a black background with sound effects) were presented in between each block to maintain infant attention to the screen.

Task 1: Face Scanning. Photographs of natural faces with a neutral expression (three male, three female). Each stimulus

measured approximately 18 × 24 cm. Each stimulus was viewed for 10s and each block contained two stimuli.

Task 2: Pop-out. Photographs of a natural face and a 'face-noise' image alongside nonsocial content against a white background in a grid-like array (Gliga et al., 2009). The nonsocial content included pictures of mobile phones, cars and birds. The 'face-noise' image is an artificial scramble of the pixels in the face-stimulus, thus having the same low-level visual properties while being unrecognisable as a face. A total of seven stimuli were presented measuring between approximately 25 × 20 cm. Each stimulus was viewed for 10s and each block contained two or three stimuli.

Task 3: Social preferential looking task contained two neighbouring photographs with each pair consisting of a real-world scene: one with social content (one or two children) and one without (no people) (Fletcher-Watson et al., 2008). A total of 12 stimuli were presented measuring approximately 27 × 19 cm. Each stimulus was viewed for 5s and each block contained four stimuli.

Statistical analysis

Looking time at AoIs, LT at the whole stimulus and TFF AoIs were analysed for each task, as measures of sustained attention and attentional priority. TFFs <100 ms were excluded: in these cases it is likely that the saccade started prior to image onset (Liversedge & Findlay, 2000). Similarly, LTs <500 ms were excluded because this was not considered a sufficient quantity of data to represent the result of a series of planned eye movements to particular AoIs. Normality was assessed using measures of skew and by visual inspection of histograms and QQ plots. For normally distributed data, mean and standard deviation (*SD*) are reported and for non-normally distributed data, the median and interquartile range (*IQR*) are reported. For group-wise comparisons of normally distributed variables independent sample *t*-test was used, and for skewed data the Mann-Whitney *U* test was used. Repeated measures ANOVA and related samples Wilcoxon signed-rank test were used to investigate within-group differences in normally distributed and skewed data, respectively.

For the face-scanning task, a difference score of LT on eyes minus mouth was calculated. For all tasks, as well as analysing raw LT scores, a proportional looking score was calculated as the ratio of LT per AoI to LT at whole stimulus [proportional looking score = $LT(AoI)/LT(\text{whole stimulus})$]. Group differences in proportional looking scores were investigated using the Mann-Whitney *U* test. To investigate differences in overall attentiveness between groups, total LT to the monitor was recorded for each task. Two-tailed *p*-values are reported and $p < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 21 (Chicago, IL).

Results

Participant characteristics

Fifty preterm and 51 term eligible infants were assessed with eye tracking. One participant born at term was excluded due to poor data acquisition, leaving 50 preterm infants and 50 term infants (Table 1 for participant characteristics).

Of the preterm group, 94% had been exposed to antenatal steroid for threatened preterm labour and 50% had been exposed to antenatal magnesium sulphate for neuroprotection. A total of 36% had bronchopulmonary dysplasia (defined as need for supplemental oxygen at 36 weeks' GA), but none was

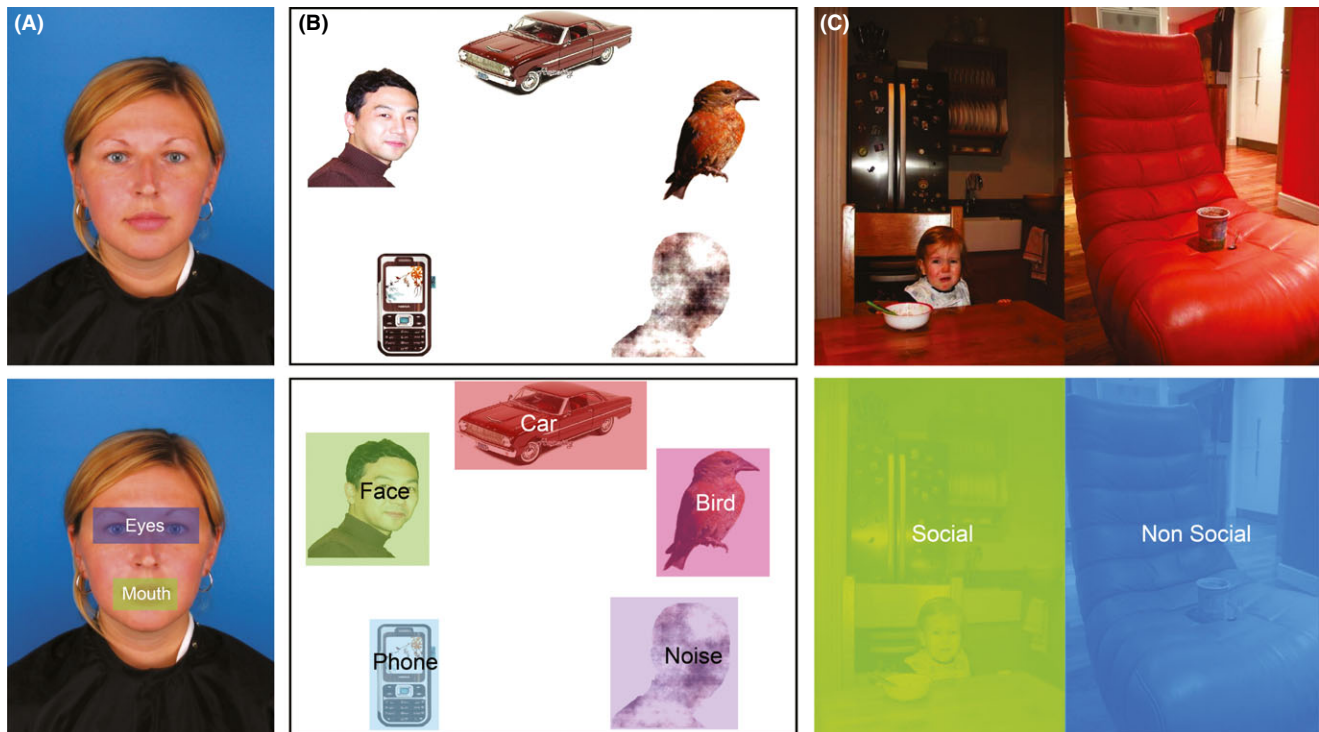


Figure 1 Examples of stimuli for each task with accompanying areas of interest (Aoi): (A) Face Scanning; (B) Pop-out; (C) Social Preferential Looking

Table 1 Demographic characteristics of participants

Characteristic	Preterm ($n = 50$)	Term ($n = 50$)
Mean gestational age at birth/weeks (range)	29 ⁺¹ (23 ⁺² –33 ⁺⁰)	40 ⁺² (37 ⁺⁰ –42 ⁺³)
Mean birth weight /kg (SD)	1.12 (0.26)	3.49 (0.66)
Median age/ months (IQR)*	7.72 (6.67–8.8)	7.85 (6.87–9.34)
Gender (M:F)	22:28	26:24
Scottish Index of Multiple Deprivation (%)	1 2–4 5	1 2–4 5
	18 68 14	8.5 40.4 51.1

IQR, interquartile range.

*Values for the preterm group corrected for gestational age at birth.

oxygen dependent at the time of assessment. One preterm infant had been treated for retinopathy of prematurity. All preterm infants passed the screening test for visual acuity at the time of assessment.

All tasks: overall eye-movement metrics

The overall proportion of trials excluded from control data because LT < 500 ms was 6% for face scanning, 7% for pop-out task and 8% for SPL. The same proportions for preterm infants were 4% for face scanning, 4% for pop-out task and 9% for SPL. These differences were not statistically significant between the groups.

There was no significant group difference in raw LT to the whole stimulus for any task with all p -values $\geq .05$ (Table 2).

Eye-gaze behaviours

Task 1: Face scanning. Both groups fixated the eyes more than the mouth (Table 2), but infants born at term had a significantly greater preference for looking at eyes than mouth. The mean difference score in raw LT (eyes – mouth) was 1.47s in controls ($SD = 1.72$) and 0.61s in the preterm group ($SD = 1.68$), $p = .013$ (Figure 2).

There was a group difference in proportional looking to eyes but not mouth: proportional LT eyes median = 0.31 for term infants versus 0.12 for the preterm group ($p = .039$). Term infants had a faster TFF the eyes than the mouth (median 1.97s vs. 4.11s, $p < .001$); and there was no significant difference in this comparison for preterm infants.

Task 2: Pop-out. Term infants showed longer raw LT to the face compared to preterm infants (median 1.34s vs. 0.8s, $p = .023$). This significant difference between groups was also apparent for the proportional looking score to the face (LT to Face Aoi / LT to whole stimulus): median = 0.34 for term infants versus 0.16 for the preterm group, $p = .036$).

There was a difference in raw LT to the Bird Aoi such that term infants fixated for longer than preterm (median 0.22s vs. 0.13s, $p = .04$), but the proportional LT to the bird was not significantly different between the groups. There were no differences in looking pattern for any other Aoi (Table 2).

TFF the Face Aoi did not differ between groups, however term infants fixated on the face-noise more quickly than preterm infants (median 2.98s vs.

Table 2 Raw looking time, proportional looking scores and time to first fixate areas of interest for each task for preterm and control infants

Task	Measure	AOI	Preterm Time/s	Term Time/s	<i>p</i> -value	Preterm Proportional looking score (IQR)	Term Proportional looking score (IQR)	<i>p</i> -value
Face-scanning	Looking Time	Eyes	0.49 (0.02–1.86)	1.24 (0.24–2.70)	.045	0.12 (0.00–0.37)	0.31 (0.07–0.51)	.039
		Mouth	0.07 (0.00–0.61)	0.06 (0.00–0.27)	.479	0.02 (0.00–0.11)	0.01 (0.00–0.06)	.388
	Time to first fixate	Whole display	5.28 (3.83–6.39)	4.96 (3.57–6.14)	.677			
		Eyes	2.74 (1.43–3.92)	1.97 (1.05–3.35)	.101			
Pop-out	Looking Time	Mouth	2.66 (1.78–4.69)	4.11 (2.24–6.42)	.058			
		Face	0.80 (0.11–1.57)	1.34 (0.62–2.49)	.023	0.16 (0.03–0.38)	0.34 (0.14–0.47)	.036
	Time to first fixate	Face-Noise	0.13 (0.06–0.30)	0.26 (0.06–0.47)	.170	0.03 (0.01–0.07)	0.04 (0.01–0.10)	.294
		Bird	0.13 (0.00–0.24)	0.22 (0.08–0.36)	.040	0.03 (0.00–0.05)	0.04 (0.01–0.08)	.074
	Looking Time	Car	0.25 (0.11–0.57)	0.21 (0.06–0.43)	.445	0.08 (0.02–0.13)	0.04 (0.02–0.09)	.125
		Phone	0.07 (0.00–0.14)	0.09 (0.04–0.21)	.094	0.01 (0.00–0.03)	0.02 (0.01–0.04)	.210
	Time to first fixate	Whole display	4.49 (3.34–5.58)	5.28 (3.92–6.41)	.063			
		Face	2.17 (1.20–3.35)	2.03 (1.22–2.97)	.640			
		Face-Noise	4.15 (1.90–5.82)	2.98 (1.74–4.26)	.045			
		Bird	3.46 (1.81–5.21)	3.59 (1.99–5.04)	.908			
Car		3.44 (1.47–4.95)	3.14 (2.05–4.79)	.828				
Phone		3.98 (2.17–6.92)	3.87 (2.54–7.15)	.970				
Social Preferential Looking	Looking Time	Social scene	1.16 (0.61)	1.50 (0.81)	.020	0.46 (0.33–0.61)	0.61 (0.45–0.68)	.012
		Nonsocial scene	0.79 (0.39)	0.74 (0.36)	.503	0.30 (0.24–0.39)	0.28 (0.20–0.34)	.141
	Time to first fixate	Whole display	2.46 (0.63)	2.63 (0.77)	.225			
		Social scene	1.49 (0.73)	1.29 (0.61)	.147			
		Nonsocial scene	1.78 (0.86)	1.63 (0.82)	.401			

Raw values for face scanning and pop-out task are reported as median (IQR), and raw values for social PL are reported as mean (SD). Proportional looking scores are reported as median (IQR). Values in bold indicate *p* < 0.05

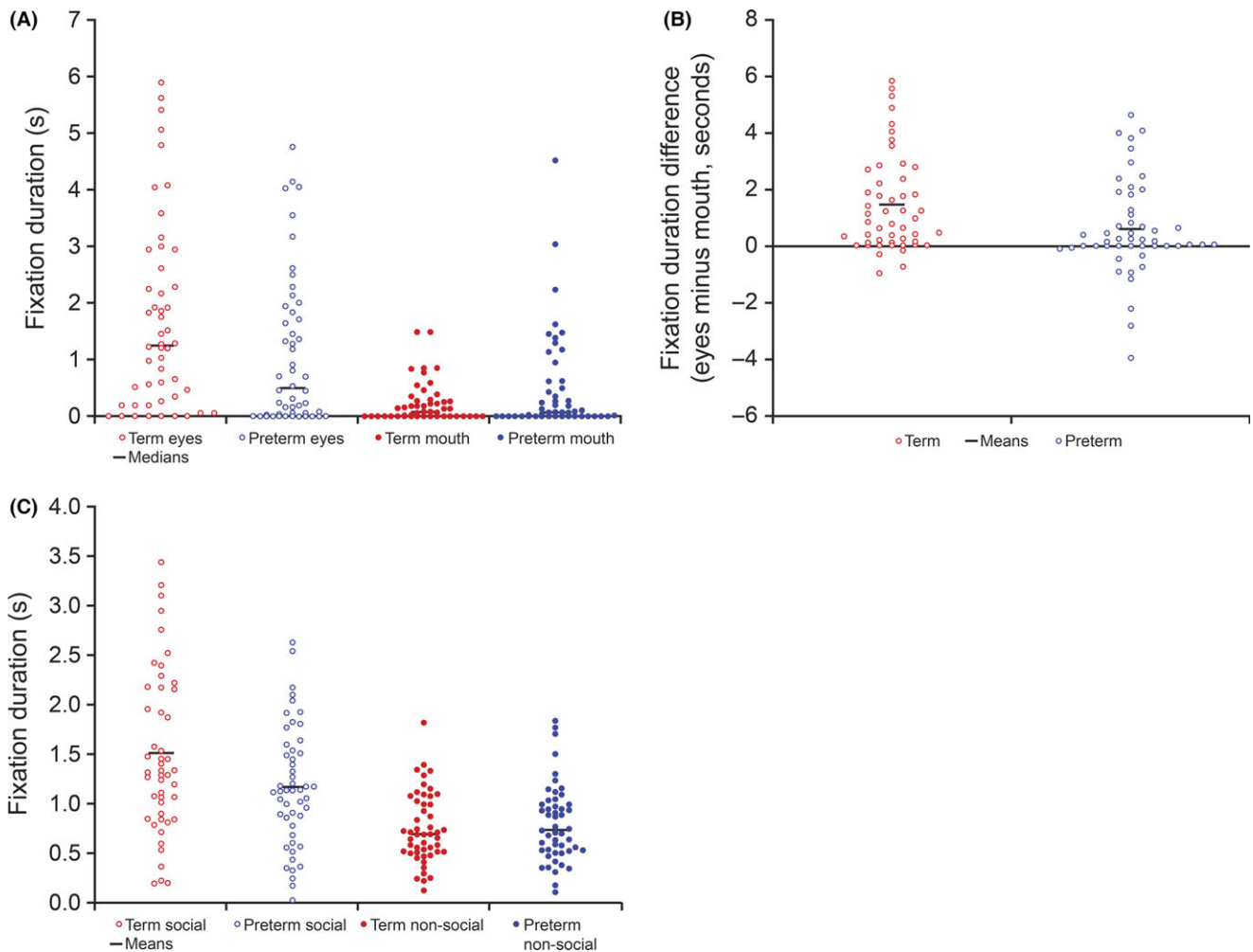


Figure 2 (A) Face scanning looking time by group and Aol; (B) Face scanning looking time with difference between eyes and mouth by group and Aol and (C) social preferential looking, looking time by group and Aol

4.15s, $p = .045$). TFF other AoIs in the array did not differ between groups.

Task 3: Social preferential looking. Term infants had a greater raw LT than preterm infants to the image within the stimulus that featured children: mean 1.5s versus 1.16s, $p = .02$ (Figure 2c). There were no differences between groups in raw LT to the nonsocial scene. Using repeated measures ANOVA, a main effect of scene was found ($F(1, 98) = 53.25$, $p < .001$) and there was a scene by group interaction ($F(1,98) = 6.40$, $p = .013$). There was no main effect of group.

There was a significant difference between groups in proportional LT for the social scene (LT to Social Scene AoI / LT to whole stimulus): median = 0.61 for term infants versus 0.46 for the preterm group, $p = .012$.

There was no group difference in TFF social or nonsocial content.

Discussion

Using eye tracking we have demonstrated that infants born preterm have a different social orienting profile to term-born peers, apparent during the first year after

birth. This fixation pattern was consistently observed across three tasks of increasing stimulus complexity. In each task, the proportion of time spent looking at socially informative content was reduced in the preterm group compared with controls. Specifically, the raw and proportional LTs of preterm infants to social content were lower compared with values measured in the control group. Analysis of the pop-out task involves five simultaneous tests, which raises the possibility that shorter LT of preterm infants to the face AoI ($p = .023$) is a false positive result. However, we consider this is unlikely because the effect size was large, and the result is consistent with the significant difference in proportional LT to social content for this task, and with observations from other tasks. We did not apply the Bonferroni correction because test statistics are known to be correlated in this task (Gliga et al., 2009), which violates an assumption of the method and introduces the likelihood of type 2 error.

We found only one difference in time to first fixate social content: term control infants fixated eyes more rapidly than mouths when viewing a static face. Of note, term infants took less time to fixate the 'face-noise' AoI in the pop-out task, which could reflect a preference for social content albeit low-level, or

failure to distinguish a real face from a scrambled face. While we checked that our preterm sample did not have visual acuity deficits, it is implausible to suppose that preterm infants were more capable than controls at detecting the difference between a real and scrambled face in peripheral vision. Thus, we conclude that both TFF observations reflect lack of general preference for looking at social (or social-like) information in preterm infants. Elsewhere, we did not find differences in time to first fixate content, or overall looking time between the groups in any task. Importantly, the proportional looking scores, which reflect attention to social content scaled by overall looking time at the stimulus was higher in term controls, and this finding was consistent across all three tasks. These scores take into account individual differences in overall looking time to the screen, which suggests that visual information processing speed and overall attentiveness do not explain the differences we observed in response to social stimuli.

The propensity to regard the mouth rather than the eyes within the static face is consistent with fixation patterns previously observed in young children either with or at risk of ASD (Chawarska & Shic, 2009) and indeed atypicalities in fixation to social content have been proposed as a potential early marker of later ASD (Young et al., 2009; Ozonoff et al., 2010; Jones & Klin, 2013; Chawarska et al., 2013). The prevalence of ASD in preterm infants is estimated at 4–8% (Hack et al., 2009; Johnson et al., 2010) therefore it is statistically unlikely that our sample contains a large number of infants who will later be diagnosed with ASD. Furthermore, we found no evidence of a split distribution or other evidence suggesting that our results were driven by a subgroup within the preterm sample. Therefore, we hypothesise that the social cognitive patterns seen in this sample may point to a lack of specificity of early social attention atypicalities for ASD. This interpretation is consistent with the observation that early atypical eye-movement behaviour initially associated with ASD diagnostic status is eliminated after adjustment for development level scores (Wass et al., 2015). In other words, some early signs of ASD may not be specific to ASD and could instead be markers of developmental delay.

It is possible that the data presented here reflect the early emergence of impaired social function, which has been described in children with very low birth weight (<1,500 g) despite normal IQ (Williamson & Jakobson, 2014), or they may herald atypical social traits that are reported in adults born preterm who do not reach diagnostic criteria for ASD (Pyhälä et al., 2014). Such traits include difficulties in processing biological motion, facial expressions or social perception (Pavlova, Sokolov, Birbaumer, & Krageloh-Mann, 2006; Wocadlo & Rieger, 2006; Indredavik, Vik, Skranes, & Brubakk, 2008; Taylor, Jakobson, Maurer, & Lewis, 2009). The significance of an early

preference to the mouth within the preterm group requires further investigation. Previous studies have suggested that attention to the mouth region is a predictor of normal language development, but the association is less clear in high-risk groups (Young et al., 2009; Lewkowicz & Hansen-Tift, 2012).

These data show that social orienting in late infancy differs between children born preterm and those born at term. Long-term follow-up of the cohort is planned, which will enable investigation of the place of atypical social orienting infancy in the development of language, and the ontogenesis of the broader preterm neurocognitive phenotype. Future research could focus on determining the sensitivity, specificity and predictive values of these measures for clinically important outcomes such as cognitive impairment or ASD. If measures of early social cognitive impairment are found to have high positive or negative predictive values for important clinical outcomes then they could have a role in diagnostic pathways, or be used to stratify risk status and provide a basis for targeting early interventions designed to improve outcome. Inattention and distractibility are two common features also associated with preterm birth (Hille et al., 2001) and success has been previously demonstrated in improving attentional control among infants under 12 month using eye tracking (Wass et al., 2011). This raises a potential use of eye tracking not just in risk stratification for early intervention trials, but also as an intervention delivery route.

Conclusion

Eye-gaze behaviours in response to stimuli depicting social content differ in infants born preterm compared with healthy term controls. These data suggest the development of social cognition is altered by preterm birth, and that eye tracking may be a useful tool for very early stratification of infants who might benefit from early interventions designed to improve neurocognitive outcome.

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Key points

- Preterm birth is a leading cause of neurocognitive impairment but early diagnosis of difficulty is limited by imprecise diagnostic tools.
- Remote eye tracking in response to visual stimuli can be used to make inference about cognitive processes in preverbal populations.
- Preterm infants have an atypical social phenotype that is present in infancy.
- Eye tracking may be valuable for early stratification of preterm infants at risk of impairment who may benefit from early interventions designed to improve outcome.

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