Diminished socially selective neural processing in 5-month-old infants at high familial risk of autism

Ricarda Braukmann,1,2 Sarah Lloyd-Fox,3,4 Anna Blasi,3 Mark H. Johnson,3,4 Harold Bekkering,2 Jan K. Buitelaar1,5 and Sabine Hunnius2
1Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands
2Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, P.O. Box 9104, 6500 HE Nijmegen, The Netherlands
3Centre for Brain and Cognitive Development, Birkbeck, University of London, Cambridge, UK
4Department of Psychology, University of Cambridge, Cambridge, UK
5Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands

Keywords: autism spectrum disorder, functional near-infrared spectroscopy, infant, social stimuli

Abstract
The social and communicative difficulties that characterize autism spectrum disorder (ASD) are considered the most striking feature of the disorder. Research has reported that individuals with ASD show abnormalities in the brain regions associated with the processing of social information. Importantly, a recent study using functional near-infrared spectroscopy (fNIRS) found the first evidence of atypicalities in the neural processing of social information in 4- to 6-month-old infants at high familial risk of ASD. These findings provide an important step in the search for early markers of ASD and highlight the potential for neuroimaging techniques to detect atypical patterns of neural activity prior to the manifestation of most behavioural symptoms. This study aimed to extend the findings of reduced neural sensitivity to social stimuli in an independent cohort. Twenty-nine 5-month-old infants (13 low-risk infants, 16 high-risk infants) were presented with social and non-social visual stimuli, similar to the previous experiment. Importantly, a non-social dynamic motion control condition was introduced allowing the comparison between social dynamic and non-social stimuli. We found that while low-risk infants showed activation to social stimuli in the right posterior temporal cortex, this activation was reduced in infants at high risk of ASD. Although the current sample size was relatively small, our results replicate and extend previous work and provide evidence for a social processing difference in infants at risk of autism. Future research will determine whether these differences relate to an eventual ASD diagnosis or may rather reflect the broader autism phenotype.

Introduction
The social and communication difficulties that characterize autism spectrum disorders (ASDs) are considered the most striking feature of the disorder. Many researchers have studied the atypical patterns of behaviour related to understanding others’ minds, goals and intentions that can be observed in individuals with ASD (Yirmiya et al., 1998; Baron-Cohen, 2000a; Brent et al., 2004; Boria et al., 2009; Zalla et al., 2010; Sparaci et al., 2014; Peterson et al., 2016).

In typically developing adults, the processing of social information is associated with specific brain regions including areas in the temporal lobe – in particular the superior temporal sulcus (STS), temporoparietal junction (TPJ), orbitofrontal cortex, fusiform face area (FFA), as well as the amygdala (Adolphs, 2003). Several neuroimaging studies have reported that individuals with ASD show atypical responses to the processing of social information in these social brain regions (Baron-Cohen et al., 2000b; Amaral et al., 2003; Zilbovicius et al., 2006; Pelphrey et al., 2011; Misra, 2014). Atypicalities include, for example, diminished responses to social sounds (Gervais et al., 2004) and faces (Jemel et al., 2006) as well as altered processing of biological motion (Kaiser & Pelphrey, 2012).

Cortical activation selective for social stimuli begins to develop early in infancy. Functional near-infrared spectroscopy (fNIRS) is one of the neuroimaging techniques best suited to study cortical activation in young infants (Lloyd-Fox et al., 2010, 2014). In fNIRS, measurements of change in absorption of near-infrared light...
from sensors placed on the infant’s head are used to infer cortical oxy- (HbO₂) and deoxy-haemoglobin (HHb) concentration changes associated with neuronal activation in the underlying tissue (Ferrari et al., 2004). Using fNIRS, Lloyd-Fox et al. (2009) were the first to show that – similar to adults – visual social stimuli elicit activation in the posterior temporal cortex in infants by 5 months of age. In the following years, other studies followed reporting similar early cortical selectivity to social stimuli, such as vocal sounds or social gaze cues (Johnson et al., 2005; Grossmann et al., 2010, 2013; Blasi et al., 2011; Lloyd-Fox et al., 2011b; Farroni et al., 2013). Given that neural tuning towards social stimuli is already present at such a young age, atypical information processing within social brain regions in ASD may also be visible early in infancy and could serve as a potential early marker of the disorder.

One way to study early social processing deficits in ASD is by means of prospective longitudinal studies. Siblings of children diagnosed with ASD have an increased risk of receiving a diagnosis themselves (ranging from 10 to 20%, compared to 1% in the general population, Constantino et al., 2010; Ozonoff et al., 2011). Following those infants during early development hence provides a unique opportunity to directly assess early markers of the disorder that may aid early detection, diagnosis and eventual treatment of ASD (Elsabbagh & Johnson, 2010; Bölte et al., 2013). Using such a prospective study design, Lloyd-Fox et al. (2013) investigated the processing of complex dynamic social stimuli in 5-month-old infants at risk of ASD. In their experiment, infants were presented with engaging social videos of a female actor which were compared to a non-social dynamic visual stimulus. In their experiment, infants were presented with social dynamic and non-social static visual stimuli. By contrasting social dynamic stimuli with non-social dynamic stimuli, this study is able to assess differences between high- and low-risk infants in the cortical processing of social information controlling for the amount of motion presented. Based on previous research (Lloyd-Fox et al., 2013), we expected to find diminished neural haemodynamic responses in posterior temporal cortex to social stimuli in the high-risk infants compared to low-risk controls.

Methods

Participants

All infants who participated in this experiment were taking part in a longitudinal study on the early development of autism. High-risk (HR) infants were included if they had at least one older sibling with a clinical diagnosis in the autism spectrum. For all children, a clinical report was available to the research team that was used to confirm the diagnosis of the older sibling. Low-risk (LR) infants were included if they had at least one older typically developing sibling and no family history of autism. In addition, all infants had to be born full-term (>36 weeks) to be included. The study was approved by the local medical ethics committee (Commissie Mensgebonden Onderzoek (CMO) regio Arnhem – Nijmegen), and written informed consent was given by both parents prior to the start of the experiment.

Thirty-five 5-month-old infants (16LR, 19HR) were enrolled and participated in the fNIRS experiment. Six infants (3HR) were later excluded due to poor data quality (3: 2HR), insufficient number of trials (1: LR) or experimenter error (2: 1HR). The final sample used for analysis hence consisted of 29 infants (13LR, 16HR, Table 1).

In addition to the fNIRS experiment described below, the development of each infant was assessed using the Mullen Scales of Early Learning (MSEL, Akshoomoff, 2006; Mullen, 1995). The measured signal originates. As motion-sensitive areas such as MT/V5 are located close to the posterior STS, differences in motion information between stimuli may result in a potential confound: Increased cortical activity may represent sensitivity to motion (MT/ V5) rather than the processing of social aspects of the stimuli (STS) (Lloyd-Fox et al., 2009). The previous study of infants at familial risk of ASD contrasted dynamic social stimuli with static non-social stimuli (Lloyd-Fox et al., 2013) and did not include a motion control condition. Therefore, while we believe from previous research in typically developing infants (see Lloyd-Fox et al., 2009) that the channels identified in Lloyd-Fox et al. (2013) were over the pSTS-TPJ region for the low-risk infants, we do not know whether stimulus motion could have had an impact on the observed response in the high-risk infants. By contrasting social dynamic stimuli with non-social dynamic stimuli, this study is able to assess differences between high- and low-risk infants in the cortical processing of social information controlling for the amount of motion presented.

### Table 1. Characteristics of the final sample

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age</th>
<th>ELC standard score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>13</td>
<td>49 (4.50)</td>
<td>95.62 (9.09) (74–110)</td>
</tr>
<tr>
<td>High risk</td>
<td>16</td>
<td>99 (4.63)</td>
<td>90.06 (11.22) (61–106)</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>139 (4.63)</td>
<td>93.55 (10.49) (61–110)</td>
</tr>
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</table>

Age and the MSEL Early Learning Composite (ELC) standard score are mean values with standard deviations reported in the parentheses. The range for the age and the ELC scores is reported in the square brackets. There were no significant differences between high- and low-risk infants in age (t(27) = −0.07, P = 0.55), gender (χ²(1, N = 29) = 1.88, P = 0.17) or ELC standard scores (t(27) = 1.44, P = 0.16).
MSEL is a standardized measure consisting of five scales [visual reception (VR), expressive (EL) and receptive language (RL), and gross (GM) and fine motor (FM)] which combined lead to the Early Learning Composite (ELC) standard score reflecting the overall development of the child. Importantly, we found no differences between the two infant groups for the overall ELC score ($t(27) = 1.44, P = 0.16$) as well as for any of the five distinct sub-scales (GM: $t(27) = 0.95, P = 0.35$; VR: $t(27) = 0.96, P = 0.35$; FM: $t(27) = 1.39, P = 0.18$; RL: $t(27) = 1.28, P = 0.21$; EL: $t(27) = -0.55, P = 0.58$), suggesting that our groups matched in their overall as well as domain-specific development.

**Stimulus material**

The stimulus material consisted of social and non-social (dynamic) video stimuli as well as non-social static images. The non-social static baseline images were the same stimulus material as used by Lloyd-Fox et al. (2013) and consisted of pictures of transportation devices (such as cars or helicopters). There were 19 different baseline stimulus images in total. Per baseline block, a random selection of six pictures was presented for a variable duration of 1–3 s per image. The social dynamic video stimuli were also based on Lloyd-Fox et al. (2013), and the current social dynamic condition was the same as the visual social condition of the previous study. The social videos showed a combination of actions or movements performed by a female actor. These included for instance the actor moving her eyes from one side to the other, moving her mouth or performing hand games such as ‘peek-a-boo’ (Fig. 1). There were 6 different social dynamic videos in total. Per block, one of those videos was presented to the infant. The video presentation sequence was pseudorandomized, ensuring that each of the six videos had been presented once before a video was repeated. The non-social stimuli consisted of videos from previous studies (Lloyd-Fox et al., 2009) as well as newly created stimulus materials. Videos were selected to be as similar as possible to the social stimulus videos in the amount of presented motion. The final selection of the non-social video stimulus set was based on a visual inspection of the motion patterns of the distinct social and non-social videos. Specifically, the amount of motion was estimated for each stimulus video by looking at frame-by-frame changes in the summed squared differences in red, green and blue colour channels of all pixels (cf. Schippers et al., 2010; Meyer et al., 2015). Consecutively, the motion energy was compared between the social and non-social stimuli and a selection of non-social videos was made for inclusion in the current study. The non-social dynamic videos showed a combination of moving toys or objects. These included, for instance, moving machines, spinning toys or toys that contained moving balls (Fig. 1). Similar to the social condition, the stimulus set of the non-social condition consisted of a total of 6 different videos and one video was pseudorandomly presented during each of the non-social dynamic blocks.

**Procedure**

Infants were seated in a baby carrier on their parent’s lap in a sound-proof testing booth in front of a computer screen monitor (24 inch, 16:9, 1920 × 1080 pixels). After the infants were capped with the NIRS headgear, they were presented with blocks of dynamic video clips in alternation with a non-social static baseline period (Fig. 1). Stimulus presentation was realized using MATLAB (Mathworks, Inc., Natick, MA; http://mathworks.com, Version 2011b), and infants’ behaviour was monitored online and videotaped for offline coding. If the participant disengaged from the display, the experimenter could play an attention getting sound to redirect the infant’s attention back to the screen and the experiment continued until the infant was bored or showed signs of discomfort.

**NIRS data acquisition**

Near-infrared spectroscopy data were collected using the University College London (UCL) topography system (Everdell et al., 2005) that emits near-infrared light at two wavelengths (780 and 850 nm). A custom-built headgear similar to Lloyd-Fox et al. (2013) was used to collect data from 26 channels (10 detector and 10 source optodes) which were placed over the temporal cortex at an inter-optode distance of 2 cm (Fig. 2). The headgear positioning was based on external anatomical landmarks of the infant’s head, and placement was done such that the posterior area of the headgear approximately covered the STS-TPJ area according to previous research, and a NIRS-MRI co-registration map of scalp location to anatomy developed for this age range (Lloyd-Fox et al., 2009, 2013, 2014).

**Data pre-processing**

Infants’ looking behaviour was coded offline to ensure that trials were only included in the analysis if infants had watched at least 60% of the dynamic stimulis as well as 30% of the pre- and post-stimuli static baseline (Lloyd-Fox et al., 2013). Importantly, we verified that there were no differences in looking time for the two conditions and between low- and high-risk infants (see Appendix S1).

The collected NIR attenuation data from each channel were assessed using artefact detection algorithms (Lloyd-Fox et al., 2009, 2011a, 2013) implemented in MATLAB (Mathworks, Inc., Natick, MA; http://mathworks.com, Version 2015b). In line with previous

![Fig. 1. Timeline of the experimental blocks. Infants were presented with blocks of social and non-social dynamic stimuli interspersed with a static non-social baseline block. The experiment always started with a baseline block, but whether the first dynamic block was social or non-social was counterbalanced between participants. [Colour figure can be viewed at wileyonlinelibrary.com].](image)
Data were transformed to HbO₂ and HHb concentration changes. Linear trends within each block were removed by subtracting a line defined between the first and last 4 s of each block. Next, the data were transformed to HbO₂ and HHb concentration changes using the modified Beer–Lambert law (Delpy et al., 1988) with a differential pathlength factor of 5.13 for infants (Duncan et al., 1995). Finally, a trial was rejected within a channel if HbO₂ concentrations exceeded 3.5 µM during baseline or 8 µM during the dynamic stimuli. For a channel to be included in the statistical analysis for a particular infant, at least three valid artefact-free trials were required. The number of infants that were included for a particular channel was hence variable.

Data analysis

Data analysis followed closely the analysis steps from previous studies using a similar paradigm (Lloyd-Fox et al., 2009, 2013). Hence, HbO₂ and HHb concentration changes during the dynamic video presentation were assessed within a four-second time window (10–14 s). This window was chosen based on other recent fNIRS studies (Lloyd-Fox et al., 2013; Lloyd-Fox et al., 2017; Lloyd-Fox et al., in press) and taking into account that the hemodynamic response takes time to reach its peak after stimulus onset. We chose a slightly narrower time window in comparison with previous studies (e.g. Lloyd-Fox et al., 2011b; Grossmann et al., 2013) as recent work by Lloyd-Fox et al. (2017) has shown that such a narrow window around the peak of the response provides a more robust marker of activation. Using this window, we extracted concentration changes for both HbO₂ and HHb. Although HBO₂ has a higher signal-to-noise ratio and responses are often more consistent in infants, it is recommended to report activation changes for both HbO₂ and HHb to provide a complete picture of cortical activation changes and to aid comparability between studies (Lloyd-Fox et al., 2010; Tachtsidis & Scholkmann, 2016) and we followed these recommendations in the current study.

In a first analysis step, the averaged HbO₂ and HHb concentration changes for the two dynamic conditions were compared to baseline using one-sample t-tests. To control for multiple comparisons, P-values were corrected for the number of investigated channels using false discovery rate (FDR) methods (Benjamini & Yekutieli, 2001). Channels that showed significant activation from baseline were then further investigated. Importantly, activation was considered valid if channels showed an increase in HbO₂ and/or a decrease in HHb. Channels for which HbO₂ and HHb were significantly increasing or decreasing in unison were not included in the analysis, as the signal was then considered inconsistent with the usually elicited cortical response (see Lloyd-Fox et al., 2013). For the channels that showed significant signal change from baseline, the peak change within the four-second time window was then extracted for the dynamic conditions for further comparisons. In a first step, differences between the social dynamic and non-social dynamic stimuli were assessed within the two infant groups using paired sample t-tests. Then, in a final step, group differences in response to the dynamic stimuli were assessed using independent sample t-tests.

Results

On average, infants watched 8.86 social dynamic blocks (range 3–17), 8.86 non-social dynamic blocks (range 3–17) and 16.55 static baseline blocks (range 5–35) and there was no difference in the amount of trials watched between the high-risk and low-risk infants.
Low-risk infants (upper panels) showed increased HbO2 concentration changes for the social dynamic stimuli in channel 25. High-risk infants (lower panels) showed increased HbO2 concentration changes for the non-social dynamic stimuli in channel 22. Significantly larger HbO2 concentration changes than the non-social infants in channel 25, as the social dynamic stimuli elicited significantly larger HbO2 concentration changes than the non-social dynamic stimuli (t(11) = 2.82, P = 0.02, Cohen’s d = 0.94). There were no condition differences in channel 22 (t(10) = 1.47, P = 0.17) for the low-risk infants. Importantly, for the high-risk infants, no condition differences were found for either channel (22: t(14) = -0.67, P = 0.51; 25: t(15) = 0.34, P = 0.74). In a last step, group differences were assessed and independent sample t-tests showed that the HbO2 response to social dynamic stimuli in channel 25 was significantly larger for the low-risk infants compared to the high-risk group (t(26) = -2.22, P = 0.04, Cohen’s d = 0.87, Fig. 3). There were no group differences for the non-social dynamic stimuli in channel 25 (t(26) = -0.09, P = 0.93), and no group differences were found for channel 22 for either condition (social: t(24) = -0.57, P = 0.57, non-social: t(24) = -0.67, P = 0.51).

Differences in cortical responses between channel 22 and channel 25

As both channels 22 and 25 are located over the pSTS-TPJ region, we would have expected similar patterns of results for these two channels, rather than the group and condition-specific difference reported above. To investigate whether patterns of activation were indeed different for the two channels, we conducted an additional post hoc analysis comparing activation in channel 22 and channel 25. A 2 x 2 repeated measures ANOVA was performed for each of the infant groups separately, using channel (Ch22, Ch25) and condition (social, non-social) as within subject factors. For the low-risk group, we found a main effect of condition (F(1,10) = 10.46, P < 0.01), indicating that HbO2 responses for the social condition were overall larger than responses in the non-social condition. The main effect of channel (F(1,10) = 2.31, P = 0.16) and the interaction effect were not significant (F(1,10) = 0.50, P = 0.50) for the low-risk infants. For the high-risk group, there was no significant main effect of condition (F(1,14) = 1.27, P = 0.28) or channel (F(1,14) = 2.56, P = 0.13), and the interaction effect did not reach significance either (F(1,14) = 2.53, P = 0.13). These results suggest that for both infants, the two channels did not differ significantly from each other. Moreover, the finding that a main effect of condition is present for the low-risk group but not for the high-risk group is in line with the results reported in the main analysis showing increased posterior temporal cortex activation for social compared to non-social dynamic stimuli in the low-risk controls only.

Fig. 3. Results of the analysis comparing cortical activation to dynamic social (left) and non-social stimuli (right) with respect to the non-social static baseline. Low-risk infants (upper panels) showed increased HbO2 concentration changes for the social dynamic stimuli in channel 25. High-risk infants (lower panels) showed increased HbO2 concentration changes for the non-social dynamic stimuli in channel 22. Significant group differences were found in channel 25, indicated by the black circle. [Colour figure can be viewed at wileyonlinelibrary.com].
Initial decrease in activation in the high-risk infants

In the time courses displayed in Fig. 4, an initial decrease in the HbO₂ response for both the social and non-social conditions seems to be visible in channel 25 for the high-risk infants. To investigate this response further, we performed an additional post hoc analysis testing for activation from baseline using a 3–7 s time window surrounding the minimum of the response visible for the high-risk infants in Fig. 4. This analysis revealed that both dynamic conditions indeed elicited a significant decrease in HbO₂ in channel 25 for the high-risk infants (social: \( t(15) = -2.18, P = 0.046, \) uncorrected; non-social: \( t(15) = -3.57, P = 0.003, \) uncorrected). No significant differences from baseline were found for HHb (social: \( t(15) = 1.37, P = 0.191, \) uncorrected; non-social: \( t(15) = 0.046, \) uncorrected).

Discussion

Previous research found that 5-month-old infants at high risk of developing autism spectrum disorders show reduced neural sensitivity to social stimuli (Lloyd-Fox et al., 2013). In the present study, a similar experimental design was implemented and our results extend the original findings. In line with our hypothesis, low-risk infants showed significant activation over right posterior temporal cortex in response to social stimuli, whereas this response was not significant in the high-risk infants. Importantly, we compared social and non-social dynamic stimuli which were similar in the amount of motion in the stimulus display. This contrast enabled us to assess whether activation of the posterior temporal cortex was modulated by the social aspects rather than representing activation originating from motion-sensitive brain regions. Confirming our hypothesis, low-risk infants showed a socially selective cortical response in the right posterior temporal cortex: HbO₂ concentration changes were larger in response to the social dynamic than the non-social dynamic condition, suggesting that the reported activation indeed originates from regions involved in the processing of social information (i.e. pSTS-TPJ, see also Lloyd-Fox et al., 2009). In contrast, social dynamic stimuli did not elicit any significant cortical activation in the high-risk infants. Rather, we found significant activation for the non-social condition in the right posterior temporal cortex with respect to baseline for this infant group. Similar activation from baseline to non-social dynamic stimuli has also been reported previously in typically developing infants (Lloyd-Fox et al., 2009) and is likely due to the more engaging nature of the dynamic stimuli compared to the static baseline. Although it is interesting that the activation to the non-social condition in the high-risk infants did survive FDR correction, whereas the social activation did not, it is important to note that we did not find significant differences between the social and non-social stimuli. Rather, the time courses of the HbO₂ responses shown in Fig. 4 appeared very similar for both conditions. These results suggest that both conditions were processed similarly by the high-risk infants and that the socially selective processing visible in the low-risk infants was diminished in the at-risk group.

Our findings complement previous studies reporting early social processing differences in at-risk infants compared to typically developing controls (Elsabbagh et al., 2012; Lloyd-Fox et al., 2013; Jones et al., 2016). Moreover, our results are in line with previous work in older individuals with ASD showing atypical social processing (Gervais et al., 2004; Jemel et al., 2006) and attentional orientation (Klin et al., 2009), as well as difficulties in the integration of complex dynamic social information (Shah et al., 2016). It has been theorized that the atypicalities in social processing observed in ASD may be the result of an early failure to orient towards social information (Jones et al., 2008; Johnson, 2014). Typically developing infants show an early bias drawing their attention towards socially relevant stimuli, like faces (Morton & Johnson, 1991; Farroni et al., 2002; Johnson, 2005). The interactive specialization theory postulates that the cortical social brain network emerges through an interaction of those early attentional biases and environmental experiences. Abnormalities in the bias to orient towards socially

Fig. 4. Averaged Haemoglobin concentration changes for the social and non-social dynamic condition for the low-risk (LR, upper panels) and high-risk (HR, lower panels) infants in channel 25 (left) and 22 (right). Time point 0 represents the onset of the dynamic video block, and the dotted window shows the time window on which the statistical comparisons are based. Group differences are indicated by the asterisk. [Colour figure can be viewed at wileyonlinelibrary.com].
relevant stimuli in ASD may hence lead to a cascade, disrupting
typical developmental processes (Johnson, 2001, 2011). There is an
ongoing debate about this hypothesis as several studies have
recently reported typical patterns of attention to social stimuli in
young infants at-risk of ASD (Elsabbagh et al., 2013; Jones & Klin,
2013). Jones & Klin (2013), for instance, showed that fixations to
the eye region during the presentation of faces were similar for 2-
month-old high-risk infants who later receive a diagnosis and low-
risk controls. The researchers reported that differences in looking at
the eyes of others only emerged later, between 2 and 6 months of
age. In contrast, Di Giorgio et al. (2016) recently reported differ-
cences in attention to social stimuli already in newborns at high risk
of ASD. Future studies will need to integrate the different findings
and provide more detailed reports of the development of social pro-
cessing in infants at risk of ASD. Our current findings, showing that
by 5 months of age socially selective cortical activation is dimin-
ished in high-risk infants, suggest that atypicalities in social process-
ing are present during the first half year of development, but more
research will be needed to assess when these deviations first
emerge.

One difference between the current study and the previous find-
ings by Lloyd-Fox et al. (2013) that needs consideration is the ex-
tent of cortical activation we observed. While previously, broader
bilateral temporal cortex activation to social stimuli was found
(Lloyd-Fox et al., 2009, 2013), significant activation was limited to
right posterior temporal cortex in the current experiment. We argue
that this difference can be explained by the stricter measures that we
applied to control for multiple comparisons. Whereas the previous
study reported uncorrected P-values, our results were corrected
using a false discovery rate approach which reduced the number of
channels that were considered significant (see Table S1 for a com-
plete report of all significant corrected and uncorrected P-values). In
addition, the sample size of the current experiment was slightly
lower than in the previous study which may have led to less power
for detecting cortical activation.

An observation we would like to further discuss is the apparent
initial decrease in the HbO2 response for both the social and non-
social conditions visible in channel 25 in the high-risk infants (see
Fig. 4). Post hoc additional analyses of this initial response revealed
that the HbO2 decreased significantly for both the social and the
non-social condition, whereas no significant differences were appar-
ent for HHb. As the two chromophores were thus not decreasing in
parallel, supporting the notion that this phenomenon may be a relevant
main effect for the low-risk group, but not for the high-
risk group, in line with the results from the main analysis.

Despite a slightly smaller sample size and more conservative
analysis approach, we replicated the expected pattern of increased
cortical activation within the pSTS-TPJ region to social stimuli in
low-risk controls which was absent in the high-risk group. Our
study thus illustrates that fNIRS is a powerful technique which is
able to detect atypicalities in brain function during early infancy.
While many of the behavourial red flags of developing ASD – such
as lack of response to own name or difficulties in joint attention –
start to emerge only around the end of the first or second year of
life (Zwaigenbaum et al., 2005; Palomo et al., 2006; Jones et al.,
2014), this study and other neuroimaging experiments have shown
group differences earlier in development (Bosl et al., 2011; Wolff
et al., 2012; Lloyd-Fox et al., 2013). We currently have no infor-
mation on whether the infants in our sample will develop typically
or receive a diagnosis within the autism spectrum disorder at a later
age. Therefore, while our results may be related to early autism,
they may also indicate a risk group effect that is unrelated to a later
ASD diagnosis. Likewise, some studies have shown that early
group differences can be present in at-risk infants (Merin et al.,
2007) while not being related to a later ASD diagnosis (Young
et al., 2009), while others have shown that early neural responses
are associated with later diagnoses of ASD (Elsabbagh et al.,
2012; Lloyd-Fox et al., in press). Whether our current results repres-
ent an early marker of ASD or rather a characteristic of the risk
group can be investigated once outcome data are available for our
sample.

At the age of 36 months, a preliminary diagnosis of ASD can be
made enabling researchers to classify high-risk participants into
groups of infants that do develop ASD (HR-ASD) and those that do
not (HR-noASD). Recent findings from a collaborating laboratory
using a similar fNIRS paradigm (Lloyd-Fox et al., 2013) suggest
that atypicalities in social processing may indeed be especially pro-
nounced in high-risk infants that receive a diagnosis of ASD at
36 months (Lloyd-Fox et al., in press). The researchers found that
HR-ASD infants showed diminished social brain network activation
to visual and auditory social stimuli compared to low-risk controls,
providing the first evidence that these neural signatures may have
the potential to be an early marker of the disorder. Their results
were based on a small sample of 5 HR-ASD infants, so it will be
important to establish whether those infants from our sample who
go on to receive a diagnosis of ASD at 36 months also show similar
patterns of atypicality. Furthermore, in line with previous prospec-
tive infant ASD research (Kaiser et al., 2010; Elsabbagh et al.,
2013), Lloyd-Fox et al. (in press) found that differences between
HR-ASD and HRD-noASD infants were not as strong as those with
LR infants, suggesting that altered cortical responses to social stim-
uli may also be present in the broader autism phenotype (BAP). The
BAP describes the finding that unaffected family members of indi-
viduals with autism share characteristics of the disorder at a subclini-
cal level (BAP, Parr & Le Couteur, 2013; Piven et al., 1997).
Getting a clearer picture of the characteristics of the BAP over
development as well as of differences that can be predictive of ASD
in the high-risk infants will greatly benefit our understanding of the

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European Journal of Neuroscience, 1–9
disorder and aid early detection and diagnosis. To enable those more detailed analyses in the future, data from larger samples will be required. Once the infants from the current study reach the age of 36 months, data can be pooled with other samples – such as the sample from Lloyd-Fox et al. (in press) – to create a large data set for further analysis.

Taken together, our findings provide compelling evidence for an early social processing difference in 5-month-old infants at risk of ASD. Future research will determine whether these differences relate to an eventual diagnosis or may rather reflect the broader autism phenotype.

Supporting Information
Additional supporting information can be found in the online version of this article:

Table S1. Results from the one-sample t-tests assessing significant changes in HbO2 and HHb with respect to baseline in the low-risk and high-risk infant group.

Appendix S1. Analysis of group and conditional differences in stimulus attention.

Acknowledgements
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115300 (EU-AIMS), resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007–2013) and EFPIA companies in kind contribution. This research is further supported by the European Union’s Horizon 2020 Marie Skłodowska-Curie ITN project BRAINVIEW (grant agreement no. 642996), The UK Medical Research Council (G0701484) and The Simons Foundation (SFARI201287).

Additional financial contributions to this project were received from the European Commission’s Seventh Framework Programme (FP7/2007–2013) INNOMED project BRAINVIEW (grant agreement no. 642996), The UK Medical Research Council (G0701484) and The Simons Foundation (SFARI201287). The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115300 (EU-AIMS), resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007–2013) and EFPIA companies in kind contribution. This research is further supported by the European Union’s Horizon 2020 Marie Skłodowska-Curie ITN project BRAINVIEW (grant agreement no. 642996), The UK Medical Research Council (G0701484) and The Simons Foundation (SFARI201287).

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The authors have no conflict of interest to declare.

Author contributions
R.B. contributed to all aspects of this experiment: design, data collection and data analyses. S.L-F & A.B. contributed to the design and data analyses. M.H.J., H.B., J.K.B. & S.H. contributed to the design. All authors (R.B., S.L-F., A.B., M.H.J., H.B., J.K.B., S.H.) contributed to interpreting the results and to writing the manuscript.

Data accessibility
Data are stored in the EUAIMS Data Repository, and requests for data should go through the EUAIMS and Euroisibs network data access policies. Please visit www.eurosibs.eu for contact details.

Abbreviations

(p)STS, (posterior) Superior temporal sulcus; ASD, autism spectrum disorder; BAP, broader autism phenotype; FDR, false discovery rate; FFA, fusiform face area; fNIRS, functional near-infrared spectroscopy; HbO2, oxy-haemoglobin; HHb, deoxy-haemoglobin; HR, high-risk; LR, low-risk; TPJ, temporoparietal junction.

References


