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Frontal cortex functioning in the infant broader autism phenotype

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ABSTRACT

Atypical attention has been proposed as a marker of the broader autism phenotype. In the present study we investigated this and the related process of inhibitory control at the youngest possible age through the study of infant siblings of children with an autism spectrum disorder (Sibs-ASD). Both attention and inhibition have been related to the frontal cortex of the brain. Nine- to ten-month-old Sibs-ASD and low-risk control infants completed the Freeze-Frame task, in which infants are encouraged to inhibit looks to peripherally presented distractors whilst looking at a central animation. The attractiveness of the central stimulus is varied in order to investigate the selectivity of infants' responses. In line with previous studies, it was found that a subset of Sibs-ASD infants had difficulty disengaging attention from a central stimulus in order to orient to a peripheral stimulus. The Sibs-ASD group also showed less Selective Inhibition than controls. However, Sibs-ASD infants did demonstrate Selective Inhibitory Learning. These results provide preliminary evidence for atypical frontal cortex functioning in the infant broader autism phenotype.

1. Introduction

Autism spectrum disorders (ASDs) are a range of developmental disorders characterized by deficits in social interaction and communication as well as restricted, repetitive and stereotyped behaviors and interests (DSM-IV-TR; American Psychiatric Association, 2000). In recent years, studies of infant siblings of children with ASD (Sibs-ASD) have provided valuable evidence on early precursors of ASD and shed light on the broader autism phenotype (BAP) in infancy. This research has been motivated by the need to understand the emergent nature of ASD through the prospective study of a group of at-risk infants (for reviews, see Barbaro & Dissanayake, 2009; Elsabbagh & Johnson, 2007; Ozonoff et al., 2008; Yirmiya & Ozonoff, 2007; Zwaigenbaum & Stone, 2008; Zwaigenbaum et al., 2009).

Sibs-ASD are at increased risk of ASD because of the genetic make-up shared with their older sibling. A genetic basis of ASD has been confirmed through converging lines of evidence (Bailey et al., 1995; Constantino & Todd, 2003; Folstein & Rutter, 1977; Steffenburg et al., 1989). The recurrence rate in siblings of children diagnosed with ASD has been estimated to be 2–10% in early studies (Muhle, Trentacoste, & Rapin, 2004; Ritvo et al., 1989), which is considerably higher than the

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0.6–1.5% incidence of ASDs in the general population (Baird et al., 2006; Baron-Cohen et al., 2009; Chakrabarti & Fombonne, 2005; Kuehn, 2007). The precise molecular and neural pathways causing ASDs remain relatively poorly understood, though some important progress has been made in identifying linkage peaks and candidate genes in recent years (Abrahams & Geschwind, 2008; Glessner et al., 2009; Losh, Sullivan, Trembath, & Piven, 2008).

The genetic risk for autism is associated with a broader phenotype that extends beyond the traditional diagnostic boundaries of ASDs to include subtler autistic-like traits (Bailey, Palferman, Heavey, & Le Couteur, 1998; Dawson et al., 2002). The recurrence rate of this broader autism phenotype (BAP) in siblings of individuals with ASD is higher than the recurrence rate of the diagnosed disorder, approximately 10–20% (Bolton et al., 1994). In family history studies, milder deficits have been found in relatives of individuals with an ASD diagnosis in all three core symptom groups that characterize the disorder (i.e., impairments in social interaction, impairments in communication, and restricted interests and behaviors) (Bolton et al., 1994; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997). Furthermore, studies using experimental paradigms and questionnaire data with relatives of individuals with ASD have found mild impairment or atypicality in domains such as social responsiveness and theory of mind (Baron-Cohen & Hammer, 1997; Constantino et al., 2006; Dorris, Espie, Knott, & Salt, 2004; Losh & Piven, 2007), pragmatic language use (Whitehouse, Barry, & Bishop, 2007), local feature or detail-focused processing (Baron-Cohen & Hammer, 1997; Happé, Briskman, & Frith, 2001), and attention/executive functions (Hughes, Leboyer, & Bouvard, 1997).

The BAP has also been investigated in infancy. From the second year of life, Sibs-ASD who go on to develop ASD show relatively clear deficits in social communication and language (Barbaro & Dissanayake, 2009; Baron-Cohen, Allen, & Gillberg, 1992; Elsabbagh & Johnson, 2007; Ozonoff et al., 2008; Zwaigenbaum et al., 2009). Earlier in infancy, studies have focused on potential differences between Sibs-ASD as a group and control infants. Deficits at this age are more subtle and inconsistent in the group as a whole, but some evidence exists of less emotional reactivity and less parent–infant synchrony, as well as atypical scanning and looking patterns in response to the face-to-face/still face protocol, a measure of infant socio-emotional responsivity (Cassel et al., 2007; Ibanez, Messinger, Newell, Lambert, & Sheskin, 2008; Merin, Young, Ozonoff, & Rogers, 2007; Yirmiya et al., 2006). We have recently demonstrated atypical neural correlates of eye gaze processing in 9–10-month-old Sibs-ASD (Elsabbagh, Volein, Csibra, et al., 2009). Studies of the ability to respond to own name in Sibs-ASD and controls during the first year of life have provided mixed results (Nadig et al., 2007; Yirmiya et al., 2006).

One area that has been investigated less extensively in the infant BAP is executive function. Executive function involves higher order cognitive domains such as decision making, working memory, focused attention, planning, and inhibitory control. Most of these functions are associated with the frontal cortex of the brain (Kramer & Quitania, 2007; Stuss, 2007). Frontal cortex abnormalities (along with other brain abnormalities) have been found in children and adults with ASD (Ohnishi et al., 2000; Schmitz, Daly, & Murphy, 2007; Shafritz, Dichter, Baranek, & Belger, 2008; Zilbovicius et al., 1995). Furthermore, the majority of behavioral studies find impairment in at least a subset of executive functions in children and adults with ASD (Hill, 2004; Kenworthy, Yerys, Anthony, & Wallace, 2008; O'Hearn, Asato, Ordaz, & Luna, 2008; Russo et al., 2007). Importantly, similar but milder deficits and atypicalities in these executive functions have been found in first-degree relatives of individuals with ASD (Hughes et al., 1997; Hughes, Plumet, & Leboyer, 1999; Ozonoff, Rogers, Farnham, & Pennington, 1993; Piven & Palmer, 1997), suggesting that difficulties in executive function might also form part of the BAP.

The relative lack of studies which have directly assessed the status of frontal cortex functioning in Sibs-ASD is most likely due to several methodological difficulties associated with investigating frontal cortex functioning at an early age (Holmboe, Fearon, Csibra, Tucker, & Johnson, 2008). Nevertheless, a few studies have provided evidence for frontal functioning in infancy using eye movements as the dependent measure (Holmboe et al., 2008; Johnson, 1995), and recent neuroimaging research has bolstered the evidence for the existence of basic frontal cortex functioning as early as 3 months of age (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Homae, Watanabe, Nakano, & Taga, 2007; Nakano, Watanabe, Homae, & Taga, 2008).

Even though frontal cortex functions such as inhibitory control have so far not been directly addressed in the study of infant Sibs-ASD, a few studies have investigated the related area of early attentional development in this at-risk group (Elsabbagh, Volein, Holmboe, et al., 2009; Zwaigenbaum et al., 2005). One task that has been used to study attention in individuals at risk of ASD is the *gap–overlap* task. In this task conspicuous peripheral targets are presented either simultaneously with a continuous central stimulus (overlap trials), or following a brief time gap after the offset of the central stimulus (gap trials). Most typical individuals at any age take longer to orient to the target in the overlap trials, thereby showing an effect of the competition with the central stimulus. Debate continues as to the exact additional mechanisms required in the overlap trials, but most accounts attribute the additional time taken to the process of "disengaging" attention from the foveal stimulus before it is possible to shift it to the peripheral target (e.g., Hood & Atkinson, 1993). The ability to disengage attention is likely made possible by early cortical development involving a network of the visual, parietal and frontal cortex (Atkinson, 1984a, 1984b; Bronson, 1974; Johnson, 1990).

Interestingly, tasks assessing this ability to disengage attention are among the few infant tasks that have been relatively consistently shown to be associated with the early BAP. One study followed a group of Sibs-ASD from 6 months to 2 years of age, at which point children were assessed on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) in order to obtain a preliminary assessment of social-communicative impairment indicative of autism. Infants who received an ASD classification on the ADOS at 24 months were found to have a slowing of reaction time to disengage from the central stimulus in the gap–overlap task between 6 and 12 months of age (Zwaigenbaum et al., 2005). Another study examined the gap–overlap effect by looking at infants' reaction time during the gap and overlap conditions relative to a baseline condition

Table 1
Sample characteristics.

Measure	Group	
	Control	Sibs-ASD
N	33	31
Male:Female	18:15	18:13
Mean age in days (*SD*)	299 (56)	304 (50)
n Excluded data (calibration error)	2	1
Characteristics of infants included in the analysis		
n All	31	30
n Calibrated	30	27
Number of trials post-calibration		
Mean total (*SD*)	54.66 (10.52)	56.93 (15.70)
Mean valid (*SD*)	46.62 (10.01)	45.81 (15.25)

Note: No significant group differences were found on any of these baseline measures (all *ps* > .2).

where the fixation target disappeared as soon as the peripheral one appeared. In this study, a group of 9–10-month-old Sibs-ASD showed poorer disengagement (in overlap trials) and less facilitation (in gap trials) than controls (Elsabbagh, Volein, Csibra, et al., 2009). Importantly, no difference between the groups was found in the baseline condition, indicating that a failure to disengage attention was at least partly responsible for the group differences observed.

Since the frontal cortex has been closely associated with attention, the development of the frontal cortex (along with other cortical areas) is likely to be associated with improvements in infants' ability to disengage and allocate their attention flexibly. Thus, the above studies of the gap–overlap effect in at-risk infants could be interpreted as indicating early frontal-executive function problems in the infant BAP. However, in order to establish this more definitively, a group of Sibs-ASD would need to be tested on tasks specifically designed to assess early frontal cortex functioning.

We have recently reported one such task, the *Freeze-Frame* task (Holmboe et al., 2008). The Freeze-Frame task was developed to measure different aspects of inhibitory control in infancy. Infants are presented with dynamic cartoon stimuli on a computer monitor and rewarded for staying focused on this stimulus while peripheral distractors are presented. In the first few trials of the experiment the duration of distractor presentation is increased in each trial until the infant has looked to the distractor on two consecutive trials; in this way infants are calibrated individually to make sure that they detect and orient to the distractors in the first place. Furthermore, by varying the attractiveness of the central stimulus, both baseline differences in distractibility and selective learning patterns across the test session can be established. It is expected that infants will be more motivated to inhibit looks to the peripheral distractors in the interesting trials than the boring trials because of the more engaging nature of the central stimulus; this has been confirmed by data from two previous studies in typical infants (Holmboe et al., 2008, 2010).

In one previous study of typical 9-month-old infants (Holmboe et al., 2008), we found that Selective Inhibition in the Freeze-Frame task was significantly correlated with performance on a well-established infant frontal cortex task, the *A-not-B* task (Diamond, 1985; Diamond & Goldman-Rakic, 1989; Piaget, 1954). Furthermore, Selective Inhibitory Learning during the task predicted performance on another frontal cortex task, the Spatial Conflict task (Gerardi-Caulton, 2000; Rothbart, Ellis, Rueda, & Posner, 2003), at 2 years of age. We also recently found the Freeze-Frame task to be sensitive to genetic variation associated with dopaminergic neurotransmission in the frontal cortex (Holmboe et al., 2010). The aim of the present study was to establish whether Sibs-ASD differed from low-risk control infants in their performance on this task. Such differences would suggest a typical frontal cortex functioning in the infant BAP.

2. Method

2.1. Participants

A total of 31 Sibs-ASD (18 boys, 13 girls) and 33 controls (18 boys, 15 girls) took part in the study. Most infants in both groups were 9–10 months old (Table 1). Infants in the Sibs-ASD group all had an older brother or sister with a confirmed clinical diagnosis of ASD. One infant had two older siblings with ASD[1]. Eight of the older siblings were half-siblings. All older siblings except two were male. Mean older sibling age was 7.3 years (*SD* = 3.7) at the time of testing. All older siblings had received a clinical diagnosis of an ASD by a qualified UK practitioner. In addition, diagnosis of the older sibling was confirmed by two expert clinicians (TC & PB) using the Development and Well-Being Assessment (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). The sample characteristics of the groups are shown in Table 1. Sibs-ASD were within the normal range on standardized measures of general cognitive and motor skills using the Mullen Scales of Early Learning, AGS edition (Mullen, 1995) (*M* = 104, *SD* = 9.6).

[1] An additional child in this family has been diagnosed with an ASD since the completion of the study (i.e., this infant now has three siblings with ASD).

Infants in the control group were recruited from the Babylab volunteer database at the Centre for Brain and Cognitive Development at Birkbeck. Standardized measures were not available for the control group but exclusion criteria for both groups included prematurity, low birth weight, medical or neurological conditions, sensory or motor problems. None of the children in the control group had first or second degree relatives diagnosed with autism.

Two infants (1 boy and 1 girl) from the control group and 1 girl from the Sibs-ASD group had to be excluded from analyses involving post-calibration data because of calibration error (i.e., the experimenter calibrated the infant more than 10 trials too late or too early). Ethical approval for the study was granted by the National Health Service London Multicentre Research Ethics Committee (Ref. No.: 06/MRE02/73).

2.2. Stimuli and procedure

The stimuli and procedure were identical to those described in Holmboe et al. (2008). Briefly, infants were presented with the stimuli on a 19-in (48.3-cm) monitor, while seated on their parent's lap. Looking behavior was monitored and recorded from an adjacent room. Whenever needed, the infant's attention was drawn to the screen using sounds. Infants were encouraged to complete at least 60 trials, but the session was stopped if the infant became fussy. On each trial, the infant was presented with a moving stimulus in the centre of the screen subtending between $10.5^\circ \times 10.5^\circ$ and $12.4^\circ \times 15.2^\circ$. Once the infant fixated the central target, a distractor appeared either to the right or the left of the target at an eccentricity of 13.5°. The distractor was a white square subtending 3.2°. To examine the effect of varying the central stimulus, the attractiveness of this stimulus was manipulated: on even numbered trials the infant was presented with varying and dynamic cartoon animations (interesting trials) and on odd numbered trials the infant was presented with a simple rotating orange star (boring trials).

The beginning of the experiment was used as a calibration phase. Thus, we progressively increased the presentation duration of peripheral distractors online for each infant until they reliably elicited saccades. At the beginning of the calibration phase the duration of the distractor was set to 200 ms and increased trial by trial in 40 ms steps whenever the infant did not look to the distractor. The duration of the distractor was fixed once the infant reached the calibration criterion, which consisted of 2 consecutive trials where the infant made a saccade to the distractor, or once a maximum stimulus duration of 1200 ms was reached. This method was used to ensure that infants detected the distractors adequately before assessing their ability to inhibit looks to the distractors. With this procedure we hoped to level out any baseline differences between Sibs-ASD and controls in the phase following calibration. Given the previous literature (Elsabbagh, Volein, Csibra, et al., 2009; Zwaigenbaum et al., 2005), we expected that Sibs-ASD would require slightly longer peripheral stimulus durations to reach the calibration criterion.

Scores on three inhibitory Freeze-Frame indices were calculated on the basis of all trials from two trials prior to calibration. The post-calibration data were then divided into three phases of 16 trials each (8 boring and 8 interesting trials). Subsequently, invalid trials were removed and the proportion of looks to the distractors in each phase and trial type was calculated. Infants had to have at least 4 valid trials in a Trial Type $\times$ Phase cell for the proportional measure to be calculated for that cell. Based on these data, the General Inhibitory Learning index was calculated by subtracting the proportion of looks to the distractors in Phase 3 from the proportion of looks to the distractors in Phase 1, across both trial types. This index is considered to be a measure of a general ability to learn to stop looking to the distractors during the task; this may be an active process or basic habituation to the distractors. The Selective Inhibition index was calculated by subtracting the proportion of looks to the distractors in the boring trials from the proportion of looks to the distractors in the interesting trials in Phase 1. This index is thought to be a measure of baseline differences in distractibility as a function of the attractiveness of the central stimulus. Finally, the Selective Inhibitory Learning index was calculated by finding the difference between the two trial types in the decrease in looks to the distractors between Phase 1 and 3. The difference measure is calculated such that a positive score on the index indicates a relatively larger decrease in the interesting trials than in the boring trials across the test session, whereas a negative score indicates a relatively larger decrease in the boring trials. The Selective Inhibitory Learning index is thought to be a measure of whether the infant can learn to selectively inhibit looks to the distractors in the interesting trials where the motivation to inhibit should be higher (Holmboe et al., 2008).

Video recordings of the infants' looking behavior were coded offline. Trials were only considered valid if the infant looked at the central stimulus throughout the trial or made a saccade to the distractor. Trials where the infant looked away from the screen during any part of distractor presentation were discarded. The groups did not differ on any baseline measure (see Table 1) including the total number of trials and the number of valid trials. Intercoder reliability for typical infants has been reported previously (Holmboe et al., 2008) and was high for both looking behavior and validity judgments. Likewise, intercoder reliability was excellent for both judgments in the Sibs-ASD group (based on data from 9 infants/520 trials): look to distractor: $\kappa = .98$; trial validity: $\kappa = .93$.

3. Data analysis and results

3.1. Calibration data

The calibration criterion was met relatively quickly for most infants. The distractor durations necessary to achieve criterion are presented in Fig. 1. Mean distractor duration for calibration was 345 ms ($SD = 168$) for the control group and 456 ms

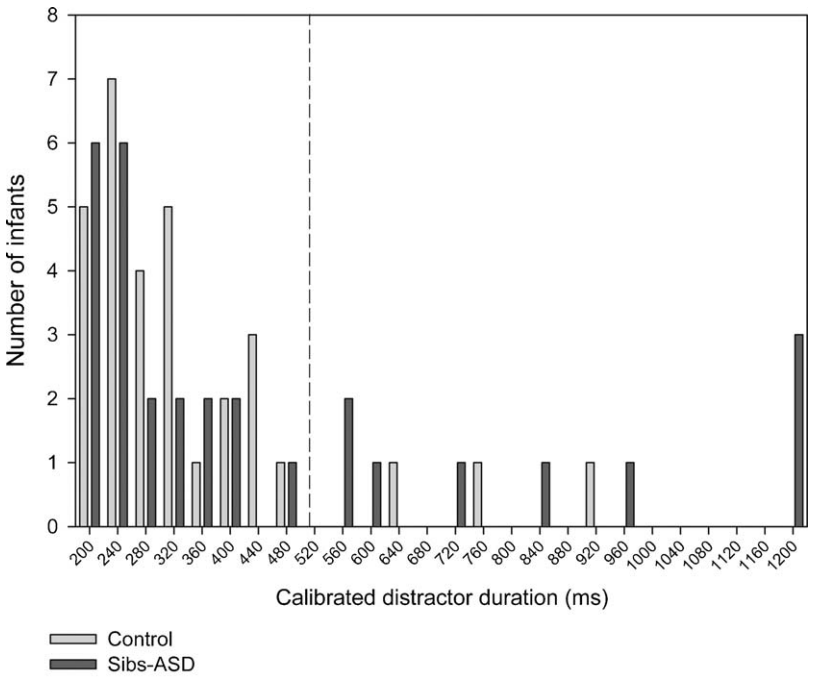

Fig. 1. Frequencies of calibrated distractor durations for Sibs-ASD and controls (the dotted line indicates the cut-off for the sticky-fixation group).

(*SD* = 320) for the Sibs-ASD group. This includes three infants in the Sibs-ASD group who reached the maximum distractor duration of 1200 ms without satisfying the calibration criterion, as well as one infant in the control group who did not calibrate within 920 ms (the session had to be stopped early because of fussiness). The mean calibration duration for the control and Sibs-ASD groups without these infants was 325 ms (*SD* = 132) and 373 ms (*SD* = 208), respectively.

As can be seen from Fig. 1 there appear to be more Sibs-ASD individuals at the longer distractor durations. Because the calibration distribution was positively skewed, and because three infants in the Sibs-ASD group reached the maximum duration, non-parametric statistics were employed to analyze the calibration data (infants who did not calibrate were assigned a calibration duration of 1200 ms). A 1-tailed significance level was used based on previous findings of disengagement difficulties in Sibs-ASD (Elsabbagh, Volein, Csibra, et al., 2009; Zwaigenbaum et al., 2005). A Mann–Whitney *U*-test showed no significant difference between groups ($U = 415.5$, $p = .24$, 1-tailed, $r = .09$). This suggests that there is no overall difference between the two groups in terms of the distractor duration at which infants calibrated in the current sample.

However, another possibility is that a subgroup of Sibs-ASD has particular difficulty disengaging from the central stimulus and therefore calibrates later or not at all. We tested this by splitting the entire infant sample into two groups based on their calibration durations: a 'sticky-fixation' group and a 'typical duration' group. Since we were interested in whether there was an over-representation of Sibs-ASD in the group which had particular difficulty disengaging from the central stimulus (and who therefore calibrated very late) when compared to control infants, we decided to use a cut-off based on the control mean and standard deviation. Thus, infants whose calibration duration was more than one standard deviation above the control mean or who did not calibrate within the session were classified into the sticky-fixation group, and those whose calibration duration was within one standard deviation of the mean or was below the mean were classified into the typical duration group. The cut-off of 512 ms is indicated with a dashed line in Fig. 1. Three out of the 31 infants in the control group and 9 out of the 30 infants in the Sibs-ASD group were classified as being in the sticky-fixation group. Chi-squared analysis using two experimental groups (Sibs-ASD, control) and two calibration groups (sticky-fixation, typical duration) showed a significant association between the two factors (Fisher's Exact Test: $p = .046$, 1-tailed). This result indicates that there is a significant over-representation of Sibs-ASD at the extreme end of the calibration spectrum compared to controls.

3.2. ANOVA

Data from infants who calibrated in the Freeze-Frame task were initially analyzed using ANOVA. The between-subjects factor was Group (Sibs-ASD and control) and the within-subjects factors were Trial Type (boring and interesting) and Phase (1, 2 and 3). Following Holmboe et al. (2008), only infants who calibrated and who completed at least 50% of the trials in each phase and trial type were included in the analysis (see Section 2). Twenty Sibs-ASD and 24 control infants had proportional data from both trial types in all three phases. Fig. 2 shows the mean and *SE* in each phase and trial type for these infants.

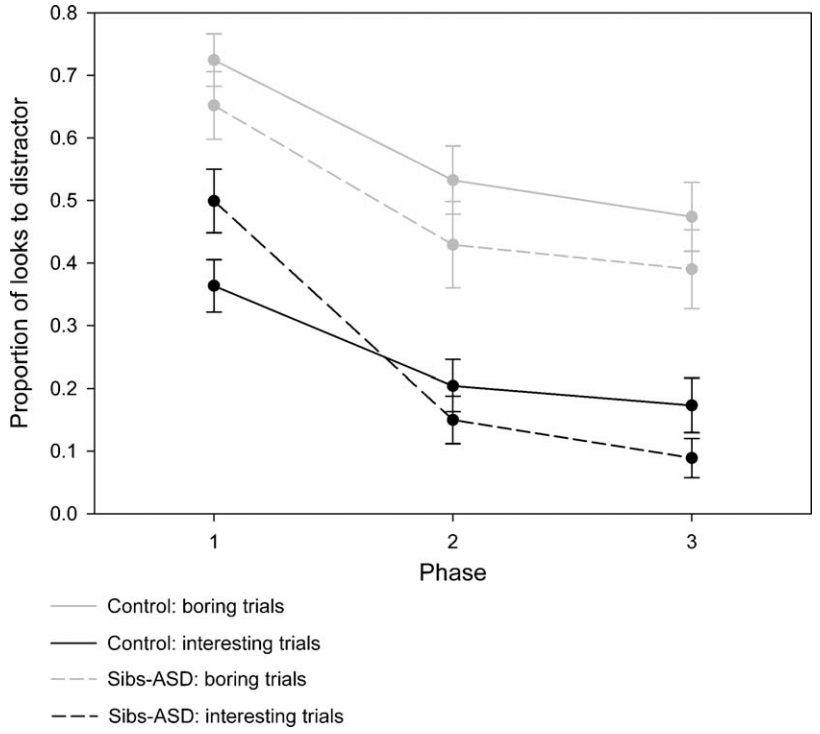

Fig. 2. Proportion (mean and standard error) of looks to the distractor in each phase and trial type for Sibs-ASD and controls.

There were highly significant main effects of Trial Type, $F(1,42) = 59.56$, $p < .001$, $\eta_p^2 = .59$, and Phase, $F(2,84) = 63.02$, $p < .001$, $\eta_p^2 = .60$, but no interaction between Trial Type and Phase, $F(2,84) = .56$, $p = .58$.

In terms of effects involving the two experimental groups, there was no significant main effect of Group, $F(1,42) = 1.01$, $p = .32$, or Group × Trial Type interaction, $F(1,42) = 1.33$, $p = .26$. Thus, among infants who calibrated, Sibs-ASD did not have an overall lower level of looking to the distractors, and like controls they generally looked less to the distractors in the interesting trials than the boring trials. However, there was a trend towards an interaction between Group and Phase, $F(2,84) = 3.03$, $p = .054$, $\eta_p^2 = .067$, and towards a three-way interaction between Group, Trial Type and Phase, $F(2,84) = 2.37$, $p = .10$, $\eta_p^2 = .053$. This suggests that Sibs-ASD and control infants differed modestly in their learning patterns across the test session. Despite the trend towards a Group × Phase interaction, post hoc tests revealed no significant differences between groups in any individual phase (all $ps > .1$). However, post hoc tests exploring the Group × Trial Type × Phase interaction indicated that Sibs-ASD and controls differed significantly in the proportion of looks to the distractors in the interesting trials in Phase 1 ($p = .046$; difference between groups: 13.6%). No other group comparisons in individual phases and trial types reached significance (all $ps > .1$).

3.3. Group comparison of inhibitory Freeze-Frame indices

Finally, Sibs-ASD and controls were compared on the three inhibitory indices used in Holmboe et al. (2008). This analysis was carried out in order to be directly comparable with the findings from the previous study. Mean scores on the inhibitory indices for each group are presented in Table 2. As in Holmboe et al. (2008), the Selective Inhibition index and the Selective Inhibitory Learning index were strongly negatively correlated, $r = -.602$, $p < .001$, suggesting that the relative decrease in the two trial types is dependent on the initial difference in looks to the distractors in the two trial types. Furthermore, as would be expected from the pattern observed in Fig. 2, Sibs-ASD scored lower on the Selective Inhibition index than did controls. This

Table 2
Scores on the Freeze-Frame inhibitory indices (mean and *SD*).

Index	Group	
	Control	Sibs-ASD
General Inhibitory Learning	.21 (.20)	.29 (.22)
Selective Inhibition	.32 (.31)	.17 (.28)
Selective Inhibitory Learning	−.04 (.39)	.15 (.33)

difference approached significance, $F(1,54) = 3.50$, $p = .07$, $\eta_p^2 = .062$. There was also a difference that approached significance between Sibs-ASD and controls on the Selective Inhibitory Learning index, $F(1,46) = 3.27$, $p = .08$, $\eta_p^2 = .068$, suggesting that infants in the Sibs-ASD group showed a larger decrease in the interesting trials than in the boring trials, whereas infants in the control group showed little difference in the amount of decline in looks to the distractors in the two trial types (see Fig. 2 and Table 2). There was no difference between the two groups on the General Inhibitory Learning index, $F(1,52) = 1.75$, $p = .19$, i.e., the overall decline in looks to the distractors across the test session was similar for the two groups.

4. Discussion

In the present study we aimed to assess differences between infant siblings of children with ASD and a control group of infants with no family history of autism on a task developed to assess frontal cortex functioning in infancy, the Freeze-Frame task (Holmboe et al., 2008). Infants were presented with animated cartoon stimuli in the centre of a screen and were encouraged to inhibit looks to peripheral distractors. Half of the trials presented an engaging central stimulus and half presented a repetitive and boring stimulus. This was done in order to assess initial differences in distractibility as a function of the attractiveness of the central stimulus as well as the relative learning pattern across the test session.

The duration of distractor presentation was calibrated for each infant to make sure that infants detected the distractors. An initial analysis established that the Sibs-ASD group and the control group did not differ overall in terms of the distractor duration needed to elicit saccades. However, infants from the Sibs-ASD group were significantly over-represented in the sticky-fixation group compared to controls, suggesting that a proportion of these infants had difficulty disengaging from the centrally presented stimulus. This is consistent with previous work demonstrating atypical visual disengagement in Sibs-ASD (Elsabbagh, Volein, Csibra, et al., 2009; Zwaigenbaum et al., 2005). Patterns of data whereby a subgroup of Sibs-ASD show a particular behavioral profile, such as a higher level of looking to the mouth compared to the eyes or less mother–infant synchrony during social interaction, have been found in other studies (Merin et al., 2007; Yirmiya et al., 2006), though a follow-up to one of these studies found that subgroup membership was not related to later ASD diagnosis (Young et al., 2009).

The analysis of the post-calibration data suggested modest effect size differences between the Sibs-ASD and control groups. Given the fact that most of these differences were just short of being significant using conventional criteria, some caution is warranted in interpreting the results. Nevertheless, since no previous studies have directly investigated potential differences in inhibitory control in Sibs-ASD during the first year of life, we will discuss these preliminary findings and provide some suggestions for future research.

The most prominent difference between groups in the Freeze-Frame task was in Phase 1 where Sibs-ASD tended to show less of a difference between boring and interesting trials, i.e., a lower score on the Selective Inhibition index, compared to controls (see Fig. 2). This is consistent with the evidence of attentional differences between Sibs-ASD and control infants using reaction time as the dependent measure (Elsabbagh, Volein, Csibra, et al., 2009; Zwaigenbaum et al., 2005). These previous studies found that Sibs-ASD take longer to respond to peripheral stimuli when engaged by a central stimulus. In the current study we found that most Sibs-ASD could respond to the peripheral distractors provided that they were individually calibrated, but they did not show the initial tendency to be more captured by the interesting trials than the boring trials to the same extent as control infants.

There are several possible interpretations of this preliminary result. One general interpretation is that Sibs-ASD are initially less able or less motivated to flexibly adapt their attention in response to environmental changes. Alternatively, the nature of the stimuli used in the experiment may be important. For example, it is possible that Sibs-ASD to some extent prefer the repetitive orange star in the boring trials. This is relatively consistent with the data since Sibs-ASD already tended to look less to the distractors in the boring trials in Phase 1 than did controls (see Fig. 2), though this difference did not reach statistical significance (only the group difference in the interesting trials in Phase 1 was significant).

Conversely, Sibs-ASD might find the interesting animations less engaging than control infants and therefore be initially more distractible in the interesting trials. The interesting trials present a range of animated objects and figures, many of them human- or animal-like, so another possibility is that Sibs-ASD are less engaged by these stimuli because some of them are social in nature. Of course these interpretations are not mutually exclusive, and both factors may play a role; i.e., compared to controls, Sibs-ASD may initially prefer a repetitive non-social stimulus over a more social and variable one. It is also possible that Sibs-ASD simply discriminate less between the two trial types at the beginning of the session.

Interestingly, the initial difference between groups did not persist during the Freeze-Frame session. The fact that the ANOVA showed a trend towards a three-way interaction between Group, Phase and Trial Type indicates that the two groups may differ in their response patterns during the task. This is also suggested by the analysis of the Selective Inhibitory Learning index which showed a modest effect size difference between groups. Thus, Sibs-ASD tended to show a larger decrease in looks to the distractors in the interesting trials than in the boring trials, whereas controls showed a similar decrease in the two trial types (Fig. 2).

This finding is not surprising given that both the current study and the study by Holmboe et al. (2008) showed a strong negative correlation between the Selective Inhibition index and the Selective Inhibitory Learning index. However it does suggest that at the end of the session the looking pattern in the Sibs-ASD group in the two trial types is similar to controls. In fact, Sibs-ASD seem to be looking slightly less to the distractors in both trial types at this point (see Fig. 2). An implication

of this finding is that Sibs-ASD are able to learn to inhibit looks to the distractors (Selective Inhibitory Learning), though baseline differences in distractibility as a function of the attractiveness of the central stimulus (Selective Inhibition) appear to be fundamentally different in this group. This again suggests that Sibs-ASD show an atypical pattern of basic attentional mechanisms.

In the study by Holmboe et al. (2008), the Selective Inhibition index was found to be significantly associated with other frontal cortex tasks in infancy and early childhood. The index was positively associated with performance on a classic infant frontal cortex task, the A-not-B task (Diamond, 1985), at 9 months of age, but also negatively related to several measures of frontal cortex functioning at 2 years of age. The Selective Inhibitory Learning index was positively related to later frontal cortex performance. Since we only administered the Freeze-Frame task in the present study, we cannot know whether Sibs-ASD would show a similar pattern of cross-sectional and longitudinal correlations; this is a question which will need to be addressed in future research. However, the fact that the Freeze-Frame task is associated with other measures of frontal cortex functioning across infancy and early childhood offers promise in investigating potential differences in developmental patterns of such functioning in the early BAP.

In conclusion, we have demonstrated some albeit marginal group differences in inhibitory control processes between infant Sibs-ASD and controls, consistent with these cognitive characteristics forming part of the BAP (Hughes et al., 1997, 1999; Ozonoff et al., 1993; Piven & Palmer, 1997). However, as the present group of Sibs-ASD have not been followed up to an age whereby diagnosis can be established, we cannot determine whether these differences may be early markers of later diagnostic or other outcomes. Either pattern of results would be of interest in helping us understand the early cognitive trajectory of the BAP, how this might relate to early behavioral and brain development trajectories, and whether such early signs might signpost later emergence of the ASD phenotype as opposed to the BAP.

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