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Neural correlates of face processing in etiologically-distinct 12-month-old infants at high-risk of autism spectrum disorder

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ABSTRACT

Neural correlates of face processing were examined in 12-month-olds at high-risk for autism spectrum disorder (ASD), including 21 siblings of children with ASD (ASIBs) and 15 infants with fragile X syndrome (FXS), as well as 21 low-risk (LR) controls. Event-related potentials were recorded to familiar and novel face and toy stimuli. All infants demonstrated greater N290 amplitude to faces than toys. At the Nc component, LR infants showed greater amplitude to novel stimuli than to their mother's face and own toy, whereas infants with FXS showed the opposite pattern of responses and ASIBs did not differentiate based on familiarity. These results reflect developing face specialization across high- and low-risk infants and reveal neural patterns that distinguish between groups at high-risk for ASD.

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Atypical processing of faces is one of the most commonly documented areas of abnormal visual attention in individuals diagnosed with autism spectrum disorders (ASD; e.g., Grelotti et al., 2002; Hubl et al., 2003; McPartland et al., 2004). Recent research indicates that these differences emerge early in development, with infants at an increased risk of ASD displaying different electrophysiological responses from low-risk infants within the first year of life (e.g., Key et al., 2014; Key and Stone, 2012; McCleery et al., 2009). Existing studies of high-risk infants have primarily focused on infant siblings of children with ASD, and it is unclear whether similar abnormalities are present in other high-risk groups. In the current study, we measured event-related potentials during a face processing task in two samples of infants at high risk of ASD – infant siblings of children diagnosed with ASD (ASIBs) and infants diagnosed with fragile X syndrome (FXS), as well as low-risk (LR) controls. We expected to observe distinct electrophysiological responses that would differentiate the high-risk ASD groups from each other and from the low-risk group.

Event-related potentials (ERPs) provide a discrete timeline of neural activation associated with face processing and reveal distinct differences in neural responses to faces in adults with ASD compared with typical adults (e.g., McPartland et al., 2004). The N170 ERP component has been most strongly associated with face detection and processing in adults and is characterized by a negative peak occurring approximately 170 ms after stimulus onset at lateral posterior scalp regions. Both typical adults and adults with ASD show greater amplitude N170 to faces compared with objects (e.g., Bentin et al., 1996; McPartland et al., 2004; Neuhaus et al., 2015; Rossion et al., 2000; Webb et al., 2010, 2012). However, adults with ASD have shown a longer latency to peak N170 than typical controls (McPartland et al., 2004, 2011). Additionally, adults with ASD do not show a right hemisphere advantage for faces, which is typically seen in adults and reflected by greater amplitude N170 at right than left lateral electrodes (McPartland et al., 2004), nor do they exhibit greater amplitude N170 responses to inverted compared with upright faces, which is exhibited in typical adults (McPartland et al., 2011; Webb et al., 2012). Thus, although adults with ASD exhibit typical increases in N170 amplitude toward faces versus objects, the temporal and spatial characteristics of the N170 response remain atypical.

Because ASD is not typically diagnosed until toddlerhood or later, recent studies have examined electrophysiological responses to faces in infants at high-risk of ASD as a means to understanding early developmental sequences of risk. This area of research has focused primarily on infant siblings of children with ASD (ASIBs), as ASD diagnosis is 18–20 times more prevalent in ASIBs than in the general population (Ozonoff et al., 2011). In addition to exhibiting increased rates of ASD, first-degree relatives of individuals with ASD have been shown to exhibit higher rates of subclinical ASD symptoms than the general population, a phenomenon known as the broader autism phenotype (BAP; Dawson et al., 2002; Losh et al.,

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2008; Ozonoff et al., 2014). Subclinical symptoms associated with the BAP may manifest through atypical cognitive and social function (Landa et al., 2012; Messinger et al., 2013). Thus, investigating early patterns of face processing among ASIBs can inform both early markers of ASD risk, as well as broader endophenotypes of ASD that manifest in clinically unaffected individuals.

Event-related potentials have been used to study the development of face processing in infant ASIBs (Elsabbagh et al., 2009; Key et al., 2014; Key and Stone, 2012; Luyster et al., 2014; Luyster et al., 2011; McCleery et al., 2009). Of primary interest to these studies are two infant ERP components strongly associated with face processing, the N290 and P400. It has been hypothesized that the N290 and P400 together function as the precursor to the adult N170 (e.g., Luyster et al., 2014). However, recent research has indicated that the N290 is more strongly linked to face processing, as cortical source analysis has localized the component to temporal and occipital brain regions including the middle fusiform gyrus (Guy et al., 2016).

Like the N170, the N290 is a negative ERP component that occurs over lateral posterior electrodes and is characterized by greater amplitude to faces than other classes of stimuli (Halit et al., 2004; Guy et al., 2016). The results of a recent study examining N290 responses in conjunction with infant heart rate-defined phases of attention indicate that sustained attention may further contribute to the differentiation of face and toy stimuli in 4.5-–7.5-month-old infants (Guy et al., 2016). This typical pattern of greater amplitude responses to faces than objects has also been observed in ASIBs (McCleery et al., 2009). However, ASIBs showed a shorter latency N290 response to objects than faces, whereas LR infants showed a trend of responses in the opposite direction (McCleery et al., 2009). Additionally, research conducted with LR and ASIB infants has indicated that N290 amplitude may be sensitive to stimulus exposure (Key and Stone, 2012; Luyster et al., 2014), although several studies of 4.5- through 12-month-old LR infants (de Haan and Nelson, 1997, 1999; Guy et al., 2016; Luyster et al., 2011; McCleery et al., 2009) and ASIB infants (Luyster et al., 2014; McCleery et al., 2009) have failed to find a significant effect of stimulus familiarity on N290 amplitude. Although the N290 is relevant to ASD due to its association with face processing, the limited ERP studies in ASIBs to date have failed to identify consistent group-specific differences related to ASD risk on N290 amplitude, latency, or topography.

The P400 is a positive component that is seen over occipital electrodes (de Haan et al., 2003). Research conducted with low-risk infants has reported shorter latency P400 responses to face stimuli than other classes of stimuli (de Haan and Nelson, 1999; Halit et al., 2004; McCleery et al., 2009). McCleery et al. (2009) found that 10-month-old ASIBs did not demonstrate this face processing advantage and exhibited slower P400 latencies to faces than LR infants. Differences in P400 amplitude and latency have been reported based on stimulus exposure, such that LR and ASIB infants showed greater P400 amplitude to a stranger's face than their mother's face, but only LR infants showed longer P400 latency to the stranger's face than their mother's face (Key and Stone, 2012). These studies indicate that the investigation of the P400 may be informative to the examination of atypical face processing in ASIBs during infancy.

Additionally, the Negative central ("Nc;" Courchesne et al., 1981) is an ERP component that is relevant to the examination of infant face processing and that has been examined in studies of ASIBs. The Nc is a negative ERP component seen from 350 to 750 ms after stimulus onset at frontal and central midline electrodes. The Nc is evident in response to a variety of visual stimuli. It is greater in amplitude in response to salient or novel stimuli and during heart rate defined stages of attention (de Haan and Nelson, 1997, 1999; Guy et al., 2013; Guy et al., 2016; Reynolds et al., 2010; Richards, 2003; Webb et al., 2005). In several studies of face processing in the first year of life, Nc amplitude has been reported to be greater in response to an infant's mother's face than a stranger's face (e.g., de Haan and Nelson, 1997, 1999; Luyster et al., 2014; Webb et al., 2005). However, additional research including ASIBs and LR infants suggest variable patterns in response to these stimuli across age and risk status. Key and Stone (2012) found that 9-month-old LR and ASIB infants showed greater amplitude Nc responses to a stranger's face than their mothers' faces. This effect was replicated in a separate cohort of 12-month-old infants and was stronger in LR infants, as a larger proportion of LR infants demonstrated greater Nc amplitude to a stranger's face than their mother's face (Luyster et al., 2011). However, a recent longitudinal examination of LR and ASIB infants from 6 to 36 months of age found that LR infants consistently showed greater Nc amplitude to their mother's face than a stranger's face, but ASIBs did not respond differentially across ages (Luyster et al., 2014). Overall, these studies suggest that the Nc may be sensitive to emerging differences in attention to salient and novel faces among ASIBs.

Notably, these extant electrophysiological studies of face processing in high-risk infants have exclusively focused on ASIBs, and no studies to date have contrasted patterns of face processing with other high-risk groups such as infants with ASD-associated genetic syndromes. Fragile X syndrome (FXS), a single gene trinucleotide (CGG) repeat disorder located on the *FMR1* gene (Xq27.3), affects approximately 1 in 3700–8900 males (Coffee et al., 2009; Crawford et al., 2001; Hunter et al., 2014). FXS is the most common known genetic cause of ASD, accounting for approximately 5% of cases (Hagerman et al., 2008), with co-morbidity of ASD with FXS associated with deleterious phenotypic effects (Bailey et al., 2008; Hatton et al., 2006; Loesch et al., 2007). The relation between FXS and ASD is well established, with 60–74% of FXS cases meeting criteria for ASD (Clifford et al., 2007; Harris et al., 2008; Kaufmann et al., 2004; Philofsky et al., 2004). There is considerable interest in studying the association of FXS and ASD due to both the clinical consequences of their co-occurrence and potential to increase understanding of ASD (Budimirovic and Kaufmann, 2011). Controversy exists, however, regarding the shared phenomenology across these two etiologically distinct disorders, as some studies indicate a high degree of concordance (Bailey et al., 1998; Dissanayake et al., 2009; Rogers et al., 2001), yet others report distinct neurobiological pathways and behavioral presentations. For instance, Rogers et al. (2001) compared the development of toddlers diagnosed with FXS, ASD, and developmental delay and found that half of the toddlers with FXS were nearly identical in ASD related behavior and symptoms to the toddlers with ASD, while the other half of the FXS sample scored very similarly to the toddlers with developmental delay. Given the complex, overlapping symptom profiles associated with FXS and ASD, examining the early emergence of ASD-associated features in FXS may inform early risk factors specific to FXS, as well as broader heterogeneous pathways of ASD emergence (McCary and Roberts, 2013).

Relative to ASIBs and those diagnosed with ASD, few studies have examined the development of face processing in FX. Farzin et al., 2009 found that adults with FXS made fewer fixations to faces than control adults during a passive face viewing task, but fixation patterns were not significantly correlated with symptoms of ASD. In a neuroimaging study, adults with FXS or ASD and control participants were asked to determine whether photographs of faces were emotional or neutral (Dalton et al., 2008). FXS and ASD groups exhibited similar emotional recognition accuracy, and demonstrated decreased activation of the fusiform gyrus relative to controls. Decreased fusiform gyrus activation in individuals with FXS has been reported elsewhere (e.g., Garrett et al., 2004), and could indicate that face processing is less automatic in FXS compared with typical adolescents and adults. Although face processing has not been examined in infants with FXS, previous research has

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