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Event Related Potentials in the Understanding of Autism Spectrum Disorders: An Analytical Review

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Abstract In this paper we critically review the literature on the use of event related potentials (ERPs) to elucidate the neural sources of the core deficits in autism. We review auditory and visual ERP studies, and then review the use of ERPs in the investigation of executive function. We conclude that, in autism, impairments likely exist in both low and higher level auditory and visual processing, with prominent impairments in the processing of social stimuli. We also discuss the putative neural circuitry underlying these deficits. As we look to the future, we posit that tremendous insight can be gained by applying ERPs to the definition of endophenotypes, which, in turn, can facilitate early diagnosis and the creation of informed interventions for children with autism.

Keywords Event related potential (ERP) · Autism · Auditory processing · Visual processing

Since autism was first described by Kanner over fifty years ago (Kanner 1943), the neurobiology of this disorder has become the focus of intense scientific investigation. While extensive efforts have been made in describing the behaviors that define autism, only in recent years has progress been made to elucidate the underlying neural circuitry involved in autism, through structural and, more recently, functional neuroimaging. Through these studies has come a heightened interest in aberrant neural circuitry in autism. Of the neuroimaging tools that have been used to elucidate brain circuitry, functional electrophysiology

stands alone in capacity to define early (i.e. in infancy) neural markers and endophenotypes. This technique, therefore, warrants further scrutiny.

Using functional electrophysiology, defined by evoked potentials and then by event related potentials (ERPs), researchers have begun to elucidate sources of the core deficits in autism by focusing first on fundamental impairments in sensory processing and then linking these impairments to deficits in social cognition that may define this disorder. While the field is most robust in the auditory domain, literature also exists on visual perception, with a few studies also addressing executive function. What has been compelling in ERP research is a genuine effort to electrophysiologically characterize the essential behavioral and cognitive traits that define autism.

In this review we first will introduce the technique of ERP and its potential utility in studying a behavioral disorder like autism. We will briefly review evoked potentials in autism research and then move on to ERPs. We will explore the areas in which major insights have been gained in the realms of auditory and visual processing, from low-level perception to higher-level social and cognitive processes, as well as in executive function. We then will look to the future and discuss the insight that could be gained by applying ERPs to the creation of endophenotypes, and to the definition of early neural markers, with the ultimate goal of using ERPs to guide phenotypically-driven, targeted therapies.

Event-Related Potentials: Background

ERPs represent transient changes in the brain's electrical activity in response to the presentation of a stimulus or event. ERPs are embedded in the ongoing electroencephalogram (EEG) and are recorded from the scalp surface. Deflections

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in the EEG are extracted by means of filtering and signal averaging in order to eliminate background noise and background EEG rhythms. ERPs consist of characteristic components that span time, ranging from early components beginning at 50 ms to components as late as 600–1,000 ms. Each component is labeled with a “P” (for positive) or “N” (for negative), and either the latency from stimulus onset or the order in which the component is observed (e.g., N200 or N2 is a negative component that occurs approximately 200 ms after stimulus onset; it is also the second major negative component to occur in the train of components). Early components reflect basic sensory processing of stimuli, while later components reflect the perceptual and cognitive processing of stimuli (Banaschewski and Brandeis 2007; Picton and Hillyard 1988). The exact timing of early versus late components depends largely on the question being asked and the modality being studied, but generally components in the first 100–200 ms are considered early, reflecting lower level processing, while those after 200 ms represent higher level processing.

ERPs have excellent temporal resolution and, as a result, represent covert cognitive processing that may not be evident in overt behaviors. Therefore, they provide insight into the neural mechanisms that underlie cognition and behavior. This is particularly helpful when there appears to be no overt difference in a measured behavior between groups despite the supposition that the neural substrate underlying that behavior may, in fact, be different. Additionally, ERPs are non-invasive and do not require sedation. In many cases, they also require minimal language and motor skill, making them ideal for a pre- or non-linguistic child, or a child with limited motor skills. In fact, through ERPs researchers have gained tremendous insight into normal social, cognitive, and perceptual development (de Haan 2008; DeBoer et al. 2004).

The major disadvantage of ERPs is their relatively poor spatial resolution. Subcortical sources, or components that are derived from multiple cortical sources, may not find accurate spatial representation in the ERP. While source analysis, magnetoencephalography (MEG), and sometimes depth electrodes have been used to add spatial resolution to traditional ERPs, the quality of data is still inferior to those gained by other neuroimaging tools such as MRI. Compared to other non-invasive neuroimaging techniques, ERP has similar spatial resolution to Near Infrared Spectroscopy (NIRS), which can detect changes in oxygenation in areas of cortex that can be reached by the length of the laser probe. Several labs are beginning to use NIRS as another tool to investigate developmental disabilities such as autism and, in the future, NIRS may be coupled with ERP to provide further information about neural processing in these populations (Aslin and Mehler 2005; Mehler et al. 2008).

Despite the limitations in spatial resolution with ERPs, we can make informed inferences about the neural sources of ERP components based on the presumed source of the behavior being tested. For instance, in a paradigm that requires explicit memory, one could assume that at least part of the generated ERP component reflects hippocampal function. Researchers have gone one step further by studying ERP paradigms in patients with specific brain lesions in order to assess the changes in the components when a particular brain structure is damaged or dysfunctional (Nelson et al. 1991). Throughout this review, we discuss the presumed neural sources of the ERP components presented in order to draw some preliminary conclusions about the neural structures and circuits that may underlie the behavioral differences seen in autism. However, it is important to note that the localization of ERP components to specific neural structures/circuits relies on a number of assumptions (based on the nature of the task and data from other imaging modalities). Given that scalp potentials likely reflect the concurrent activity of multiple neural generators, both subcortical and cortical, such localization must be accepted cautiously.

The use of ERPs in the investigation of autism has a rich and long history, perhaps reflective of the fact that some of the earliest theories about autism emphasized abnormalities in perception. In a seminal paper, Ornitz et al. (1968) concluded that the fundamental deficit in autism was an inability “to maintain constancy of perception” (Ornitz et al. 1968). Several years later, based on clinical observation of a large cohort of children, Ornitz postulated that the source of this perceptual disturbance was, at least in part, rooted in the brainstem or midbrain, particularly the areas affecting vestibular and auditory function (Ornitz et al. 1974; Ornitz and Ritvo 1976).

In the following sections, we discuss what we have learned from ERPs about the perceptual disturbances and related impairments in social cognition in autism. We first explore the auditory realm, and then discuss visual processing. For each modality we first discuss what has been learned about basic (“lower-level”) sensory processing, then move on to our understanding of attention and cortical processing (“higher-level”) in each of these modes. We then turn our attention to social cognition in each modality (speech and language processing in the auditory realm and face processing in the visual realm). Finally, we present the studies that have used ERPs to explore executive function in autism. Throughout this review we consider the insight that the ERP findings provide regarding the neural circuitry underlying the behaviors being studied. As it is not feasible to be exhaustive in our review of this vast literature, we have comprehensively selected papers that best represent the findings in each perceptual and cognitive modality.

Auditory ERPs

The cortical processing of auditory stimuli requires sound feature encoding, then auditory discrimination, and then attention to the stimulus (from involuntary switching to voluntary switching in the event of a required response). The simplest paradigms used to elicit auditory ERPs consist of the presentation of sounds at a steady rate. A second level of complexity is achieved by varying stimulus frequency, intensity, pitch, and location. These paradigms do not require a behavioral response and therefore can be performed feasibly in cognitively impaired or very young children. The next level of difficulty is introduced by requiring the participant to make a response to a stimulus. Most studies of this type have used a standard oddball paradigm. An example of a classic oddball paradigm is one in which a *frequent* stimulus is presented 80% of the time, a rare, *target*, stimulus is presented 10% of the time, and then a third *novel* stimulus is presented 10% of the time. The participant is instructed to respond each time s/he hears the target stimulus. ERP responses to frequent, target, and novel stimuli are recorded. A specific oddball paradigm known as the “Auditory Choice Reaction Time” (ACRT) has been used by several researchers in order to assess response to novelty as well as auditory attention (Oades et al. 1988, 1990).

Low-Level Auditory Processing

In infants and young children, the ERP waveform to repeated sounds consists of P1 and N2 peaks, while in adults it is characterized by a P1–N1–P2 complex. These components reflect the pre-attentive detection of sound and the temporary encoding of physical stimulus features. Therefore, amplitude and latency of components vary based on the frequency and intensity of the sound stimulus. (Ceponiene et al. 2002; Lepistö et al. 2005). Studies using depth electrodes, source modeling, and MEG have found that the N1 is generated primarily from the bilateral supratemporal cortex, but also from parietal and frontal cortices (Brazdil et al. 2005; Reale et al. 2007; Smith et al. 1990). Since these components are thought to reflect primary, pre-attentive, auditory processing, it would be expected that they would be generated from primary auditory cortex, with connections to parietal and frontal lobe as sounds undergo further cognitive processing.

Several studies have shown abnormal latencies and amplitudes of these early components in autism compared to typical controls, although the nature of the differences varies across study. (Bruneau et al. 1999; Buchwald et al. 1992; Courchesne et al. 1985a, b; Grillon et al. 1989; Lelord et al. 1973; Ornitz et al. 1972; Small et al. 1971).

An early example of a study showing faster latencies in early components was by Novick (1980), who performed a “missing stimulus paradigm” with high functioning adolescents with autism, in which auditory (and visual) stimuli were presented in a regular train, with random *deletion* of stimuli being the target. Participants were asked to respond when the deletion occurred. In this study, although responses were equally accurate and rapid between the autism group and typical controls, amplitudes were smaller among those with autism (Novick et al. 1980).

Some years later, Martineau et al. (1984) performed a study in which repeated auditory and visual stimuli were presented in succession to low-functioning children with autism, compared to age matched controls. Children with autism had significantly shorter latencies of the P1, N1, P2 and P3 components (Martineau et al. 1984). In an ACRT task with high functioning children, Oades et al. found a shorter N1 latency with normal performance in autism compared to age matched controls (Oades et al. 1988, 1990). Finally, Ferri et al. (2003), in a study comparing children with autism with age-matched controls, found similar shorter latency of N1 in a standard oddball paradigm, with normal reaction times and accuracies (Ferri et al. 2003).

On the other hand, Bruneau et al. (1999) showed a longer N1c latency for children with autism compared to both age and IQ matched controls. This study was unique in that it used controls with mental retardation as well, suggesting that the difference in low level processing was not rooted in cognitive impairment alone.

Although the cognitive ability, age, and gender of the participants varied across study, as did the exact paradigms used, we can draw some preliminary conclusions from these data. Taken together, these findings suggest that while there may be differences in the speed (based on latency) and magnitude (based on amplitude) of automatic, pre-attentive, auditory processing, these differences may not affect the accuracy or speed of response to auditory stimuli. If anything, given the shorter latencies seen, one may have expected to find *faster* reaction times, suggesting that perhaps higher cognitive processing of auditory stimuli or the motor output necessary for the response might be impaired in individuals with autism. Thus, while primary auditory cortex *may be* intact, projections to hippocampus, prefrontal, frontal and parietal cortex may be impaired. However, given that there is clear evidence for ERP differences in early auditory components between autism and controls, one could also argue that there is a true impairment in low level auditory processing. With these possibilities in mind, we now discuss studies that have evaluated higher level auditory processing in autism.

Mismatch Negativity (MMN)

Clinically, children with autism seem to prefer sameness (perhaps one source of their restricted interests and repetitive behaviors), and one could speculate that this preference is rooted in an impairment in the detection of and attention to novel or salient stimuli (i.e. either being *hypersensitive* to change or being *unable* to detect change). The MMN is an ERP component that reflects novelty discrimination. Although modulated by attention, the MMN is elicited even if attention is not being paid to the stimulus, therefore it reflects pre-attentive change detection. The amplitude of the MMN is proportional to the amount of stimulus change, and typical latency is about 150–200 ms after the onset of change. The MMN's peak amplitude is in the central frontal leads. However, given its function in novelty detection and memory, the MMN likely also represents the integrity of the primary auditory cortex and its projections to hippocampus (Bishop 2007; Kujala et al. 2001; Näätänen 1992).

In the auditory realm, several studies have shown differences between autistic and typical children in MMN latencies and amplitudes to changes in pitch. In low-functioning children with autism, Gomot et al. (2006) found shorted MMN latencies to pitch change (Gomot et al. 2002, 2006), while Ferri et al. (2003) found larger MMN amplitude for pitch changes (Ferri et al. 2003). In both of these studies, controls consisted of typically developing children. There was no associated task in either of these paradigms. Seri et al. (1999) then studied MMN in children with Tuberous Sclerosis Complex (TSC) and found that the amplitudes were smaller in children with TSC and autism compared to children with TSC who did not have autism (the authors did not specify developmental level of non-autistic children) (Seri et al. 1999). These findings support the notion that there are differences, but not necessarily impairments, in the speed and robustness of auditory sensory memory in low functioning children with autism. Interestingly, in a study of high-functioning children with autism, Cepenone found normal MMNs to simple and complex tones compared to age matched controls (Cepenone et al. 2003) suggesting that perhaps the MMN may be correlated to cognitive function in autism.

While the MMN results for simple auditory stimuli are somewhat mixed, they may suggest that the differences in neural circuits necessary for pre-attentional auditory novelty detection may correlate to cognitive functioning in children with autism. Whether impairment in pre-attentive auditory discrimination contributes to lower IQ, or whether it is a reflection of aberrant neural circuitry that also causes cognitive dysfunction requires further investigation. To truly explore this hypothesis, one would need to include a control group of cognitively impaired (IQ matched) and

specifically language impaired children without autism. We will return to the MMN in our discussion of speech processing, where more studies have been performed in recent years.

Higher-Level (Cognitive) Processing: P3b and Nc

The process of selective attention, detection, and classification of sensory information has been the focus of much of the auditory ERP work in the past two decades. The P300 (with subcomponents P3a, P3b) is a component elicited when one has to discriminate an infrequent stimulus from frequent standards. It reflects the cortical processing of the probability of occurrence of a task-relevant event. Unlike the MMN, the P300 is attention dependent, and therefore reflects higher cognitive processing of stimuli. The earlier subcomponent, P3a, is largest at frontocentral sites and is elicited by rare, task-irrelevant stimuli (*non-target novels* in the oddball paradigm). Therefore, it reflects orienting and response to novelty. The later P3b, maximal at central and parietal regions, is elicited when the subject is asked to respond to a target. The P3b is thought to be triggered by events that are attention-getting or have some salience to the individual (Courchesne et al. 1989). Developmentally, the P300 appears in the third to fourth years of life. Its amplitude increases with low stimulus probability, and its latency increases with task difficulty (McCarthy and Donchin 1976; Oades et al. 1988).

Early ERP studies attention to novelty demonstrated clear deficits in individuals with autism. In two studies using a standard auditory oddball task with high functioning adolescents and young adults, Courchesne et al. (1984) found that the auditory P3b had smaller amplitudes to targets than did normal controls, suggesting that individuals with autism processed novelty differently. In a follow up study using a missing-stimulus paradigm (described previously), high functioning adolescents with autism showed a smaller P3b, despite normal performance on the task, when compared to age matched controls (Courchesne et al. 1984, 1985a, b; Courchesne et al. 1989). Two further studies by the same group showed a similar pattern of smaller P3b despite normal performance (Ciesielski et al. 1990; Lincoln et al. 1993). Taken together, these findings suggest that while there are likely differences in novelty processing, because performance is normal, individuals with autism may be using “unusual or alternate physiological processes to detect target events” (Courchesne et al. 1989).

A second component that reflects attention is the Nc, a large negative component that originates from the fronto-central cortex (Reynolds and Richards 2005). Like the P3b, the Nc is triggered by events that are important or salient to

the individual. Unlike the P3b which emerges later in childhood, the Nc has been described in early infancy and lasts through young adulthood (Courchesne 1977; Holcomb et al. 1986). In the missing-stimulus paradigm, Courchesne found that high-functioning adolescents with autism had a positive Nc instead of the negative Nc of age-matched controls. However, in a follow up, similar study, the group found no difference in the Nc between high functioning adolescents and typical controls (Ciesielski et al. 1990).

In an effort to correlate cognitive level with auditory processing, Salmond et al. (2007) performed an auditory oddball paradigm in two groups of children with autism stratified by verbal IQ. One group had a verbal IQ <85 and the other had a VIQ >85. They found that the low IQ group had a slower P3a to novelty, a smaller Nc, and a smaller P3b than the higher IQ group, suggesting that, as with pre-attentive novelty detection, the degree of difference in attention-dependent novelty processing correlates with level of cognitive impairment (Salmond et al. 2007).

Overall, these data suggest that the neural circuits necessary for higher level processing of auditory stimuli, such as novelty detection, discrimination of stimulus features, and memory of previously presented stimuli, may be aberrant in autism. The smaller amplitudes in the P300 components suggest that individuals with autism may be investing fewer attentional resources into the further cognitive processing of auditory stimuli. Furthermore, it seems that these differences may correlate with cognitive functioning. One could certainly postulate that deficits in higher level auditory processing would impair a child's ability to learn, since the acquisition of new, salient information requires attention to and interest in task-relevant novelty. As mentioned briefly in our discussion of the MMN, to explore such a hypothesis, one would need to perform these studies with IQ matched, particularly verbal IQ matched, control groups rather than with typically developing children, as it is also possible that cognitive impairment or isolated language impairment, and perhaps not autism, drives the differences in higher level auditory processing. As we will see in later sections, several studies on language and face processing have been performed using IQ matched controls and have found differences between children with autism and those with pure cognitive impairment. These studies support the hypothesis that cognitive impairment alone is insufficient to explain a dysfunction in higher level sensory processing.

Auditory Social Cognition: ERPs in Language Processing

From our review of the literature thus far, it is clear that differences in the cortical processing of auditory stimuli exist in individuals with autism, although the extent of the

impairment may vary based on level of cognitive function. We now will move to social cognition, and ask whether there is electrophysiological evidence for deficits in the processing of *speech and language*. The critical question in both speech and face processing impairments in autism is whether the deficit lies in perception itself, or in social cognition. ERPs have been used to clarify the neural bases of these areas of impairment.

Many behavioral studies have characterized and defined the deficits in communication in autism, with clear evidence that the use of language to facilitate social interaction is impaired in these children (Baron-Cohen 1988; Tager-Flusberg 1991). Several well-designed and creative ERP studies have investigated speech processing in autism and have provided us with evidence that the brain's response to speech is, in fact, impaired in individuals with autism.

One of the first studies comparing speech to non-speech processing in autism was performed by Dawson in 1988. Children with autism with varying language ability, compared to age matched controls, were presented with phonetic ("da") and piano chord stimuli. The autism group showed smaller P300 amplitudes to phonetic stimuli in the left hemisphere and central recordings, but no differences from controls in neural response to chord stimuli (Dawson et al. 1988). In a later study, Ceponiene et al. (2003) performed an auditory oddball task with three types of stimuli: simple tones, complex tones, and vowel sounds. Subjects were 6–12 year old, high functioning children with autism and age matched controls. The results showed that while the MMN was normal, the autism group had an absent P3a to vowel changes. The authors concluded that while the sensory sound processing was actually intact, there was impairment in the "attentional orienting to speech sound changes that may ultimately affect speech processing and communication" (Ceponiene et al. 2003). In a more recent study, Whitehouse and Bishop (2008) performed a similar speech and non-speech oddball task in high functioning children with autism compared to normal controls. However, in this study the question was whether attending to the stimuli affected processing, thus there was a passive condition (no task) and one active condition (children asked to respond to the deviant stimulus). Components of interest were the P1, N2, P3, N4. The investigators found that children with autism had smaller amplitudes in all components of interest to speech sounds in the passive condition, but *not* in the active condition, suggesting that speech sound encoding may be restored when voluntary attention is given to speech sounds (Whitehouse and Bishop 2008). One may propose, based on this study, that children with autism do not choose to attend to speech sounds (because of its social nature) which, in turn, directly impairs their ability to process language.

Kuhl et al. (2005) performed a study of low-functioning preschool children with autism, compared to both IQ matched and age matched controls, using an oddball paradigm with child-directed speech compared to a non-speech analog. Both ERPs and listening preference were recorded. Kuhl found that most of the children with autism showed an intact MMN to changes in non-speech sounds, but had no MMN in response to changes in speech syllables. Additionally, the majority of the autistic children preferred to listen to non-speech sounds. Those children with autism who *did* show a preference for child-directed speech over non-speech sounds displayed an *intact* MMN to speech, thus demonstrating an association between cortical processing of language and behavior (Kuhl et al. 2005).

Moving to semantic processing, which has been shown in behavioral and imaging studies to be impaired in individuals with autism (Harris et al. 2006), Dunn and Bates (2005) performed a study in which 8–11 year old high-functioning children and typical controls were presented with lists of words, half belonging to a specified semantic category (e.g., animals) and the other half from other categories. Their task was to choose targets in a particular semantic category. The components of interest were the N1c and the N4. The N1c is a subcomponent of the N1, and reflects early processing of auditory stimuli. It is modulated by the physical aspects of a stimulus and is most likely generated in the primary auditory cortex. The N4 is a late cognitive ERP component sensitive to semantic deviance from a context. It is generated when a word is not predicted by prior words. Studies have described an N4 as early as age 5, with maximum amplitude in the frontal and central leads (Bentin et al. 1985). In Dunn's study, the response times and accuracies did not differ between groups. However, N1c latency to in-category words was delayed in the 8- year-old children, but not 11- year- old children with autism. Additionally, unlike controls, the autism group did not show N4 difference between in- and out-of- category words. These findings suggest that there may be a developmental progression in the speed of cortical processing to auditory verbal stimuli and provide evidence for differences in the neural circuitry underlying the semantic processing of words in autism (Dunn and Bates 2005).

Recently, Lepistö et al. (2005, 2006) performed two parallel studies with high functioning children with autism and with Asperger's syndrome compared to age matched controls. Speech and non-speech stimuli were presented with changes made in pitch, duration, and vowel changes. MMN to pitch changes was enhanced in children with autism, and the P3a was smaller for speech sounds compared to non-speech sounds in the autism group. These findings suggest an auditory hypersensitivity to

changes in pitch and impairment in involuntary orienting to speech in children with autism. Interestingly, the authors found similar in individuals with Asperger's syndrome, despite the fact that these two groups have such differences in their language abilities (Lepistö et al. 2005, 2006).

In 2008 Lepistö's group extended their work on language processing to low functioning children with autism, as compared to typical, age-matched controls. In this study, both tones ("pitch") and speech sounds ("phonemes") were presented under two conditions, first when all other features of the stimuli were kept constant and second when constant variation with regard to irrelevant features was included. The goal was to compare the MMN elicited by pitch and by phoneme. The group found that the children with autism showed enhanced MMN amplitudes for pitch deviants in both conditions, but only showed an enhanced MMN for phoneme deviants in the constant feature condition. These findings suggest that children with autism may struggle with phoneme discrimination when the "context of the stimuli is speech-like and requires abstracting invariant speech features from varying input," which, in turn, may imply that enhanced low level auditory processing could actually interfere with higher level language processing. These findings support earlier studies, and future studies using verbal IQ matched controls may further strengthen this conclusion (Lepistö et al. 2008).

In summary, there is clearly evidence of differences between typically developing children and those with autism in language processing at a number of levels, from cortical processing of simple speech sounds to the differentiation of changes in speech sounds to semantic processing of words. In the studies that compare the processing of speech and non-speech sounds, it seems that the neural circuits responsible for processing of speech are much more affected than those responsible for simple sound processing. Thus, we may conclude that the deficits in speech processing reflect impairment in the neural circuitry necessary for attending to, discriminating, and prioritizing speech over non-speech sounds. What is quite salient is the possible role of experience in the abnormal processing of speech sounds. In the Kuhl study, children who preferred child-directed speech to non-speech had normal MMNs to speech sounds. One could speculate that an early lack of preference for speech would preclude infants from learning from these social stimuli which could, in turn, modify the neural circuitry necessary to process and attend to spoken language which, ultimately, could impair their communication skills. A similar question about experience and neural circuitry has emerged in the face processing literature, which we discuss below.

Visual ERPs

Compared to the auditory literature, fewer data exist on visual processing in autism, and most studies of visual processing have been nested within a study investigating both auditory and visual processing. Perhaps this disparity in the literature reflects the fact that one of the core deficits in autism (impaired communication) clearly implicates auditory dysfunction. However, one certainly could implicate deficits in visual processing in the development of impaired social interaction and, perhaps, restricted range of interests. In fact, the ERP studies that have been performed with visual stimuli have raised some important questions about the integrity of visual processing in autism.

Visual paradigms and components are comparable to those in the auditory domain, with most of the autism studies using visual oddball paradigms with task and no-task conditions in order to assess visual discrimination, classification and attention. Lower level (early) visual components are likely generated from occipital cortex (primary visual cortex) while higher level, attentional components, as with the auditory realm, are likely generated from frontal and parietal cortices. We first consider the data on visual processing, and then discuss social cognition, in which visual processing translates nicely to face processing.

Visual Processing

One of the first studies to suggest impairment in visual processing in autism was performed by Novick in 1979. Her group studied high functioning children with autism and age matched controls using a missing stimulus paradigm. The stimuli consisted of flashes (or absence) of light. Children were required to make a motor response when they detected a deleted stimulus. In this study, it was found that cortical responses to the missing stimuli (defined as a late positive component, the “missing stimulus potential”) in both visual and auditory domains were smaller or absent in the individuals with autism compared to typical controls, even though their responses were accurate in detecting the deletions. The authors concluded that these findings supported a defect in “information storage” (Novick et al. 1979). However, given that the responses were still accurate, one could argue that, in fact, different (yet still effective) cortical processes were used to detect and discriminate the target stimuli.

Courchesne et al. (1985a, b, 1989) published two studies in which they performed oddball paradigms using both visual and auditory stimuli in parallel, with both task and passive conditions, in high functioning adolescents and age matched controls. In the first study, visual stimuli consisted of the letters “A” and “B.” In the autism group, they found

normal P3b amplitudes, smaller N1 amplitudes, and smaller Nc amplitudes to visual novels and targets (compared to smaller Pcz, P300, P3b, N1 in the auditory domain). In the second study, visual stimuli consisted of blue squares and red squares. Results showed a frontal positive Nc component to both visual and auditory stimuli, but a relatively intact P3b in the visual domain as compared to the auditory domain. Both studies supported the presence of qualitative differences in the neurophysiological deficits in visual and auditory modalities, as well as deficits in selective attention in the processing of visual stimuli (Courchesne et al. 1985a, b, 1989). This latter finding was supported in an ERP study of selective attention by Courchesne’s group in 1990, which found impairments in visual selective attention as represented by a smaller Nc to visual targets (Ciesielski et al. 1990).

Somewhat different results were reported by Verbaten et al. (1991), who performed a visual selective-attention task in high functioning children with autism, compared to children with conduct disorder and children with mood disorders. Their group found smaller P3a and P3b amplitudes to visual target stimuli despite normal visual fixation time in the autism group only (Verbaten et al. 1991). In another study using a visual oddball task, they also found smaller P3a and P3b to deviants (Kemner et al. 1994). Then, in a third study that attempted to better localize the P3b in a visual oddball task, they found that the central and occipital P3b was smaller, while the parietal P3b was larger in high functioning children with autism. They concluded that primary deficits in sensory processing and attention to task-relevant information exist equally in both visual and auditory domains (Kemner et al. 1999). Interestingly, one study, performed in 2006 by Hoeksma, found no difference in the P300 between high functioning adolescents with autism and age matched controls. However, the paradigm used was a modified version of an oddball task in which different streams of information are given in each ear, thus more rigorously testing selective attention (Hoeksma et al. 2006).

Finally, to target visual spatial processing using ERPs, Townsend and Courchesne performed a study comparing high functioning males with autism to age matched controls. Participants were shown rows of dimly lit boxes, with filled circles presented in one box at a time. The task was to attend to the box that was outlined in blue, with the response required whenever the circle was within the blue box. Individuals with autism were less accurate than controls, particularly when targets were peripherally located. ERP data showed that the early P3a was delayed in individuals with autism, particularly when attending to peripheral stimuli, and the later P3b was smaller in amplitude in the autism group, together suggesting that visual attention to spatially varying stimuli is likely

impaired in individuals with autism (Townsend et al. 2001). Taken together, these data do point to specific differences between individuals with autism and typical controls in visual processing. As in the auditory domain, these differences are not simply downstream sequelae of primary differences in low level processing, but likely represent aberrant neural circuits necessary for higher level visual processing, namely selective visual attention, visual discrimination, and spatial orienting.

Visual Social Cognition: ERPs in Face Processing

The neural development of face processing has been well defined by ERP studies over the past several decades. Briefly, visual preference for faces is present in the first few days of life, and from 3 to 6 months infants gain the ability to distinguish familiar from unfamiliar faces, differentially process inverted from upright faces, exhibit a right hemisphere bias for processing faces, and differentiate emotional expressions (Cassia et al. 2006; de Haan and Nelson 1997, 1999; Nelson and De Haan 1996; Webb et al. 2006; Webb et al. 2005; Webb and Nelson 2001). Face specific ERP components include the N290 and the P400 in early infancy, and then the N170 in later childhood. The N290 and P400 may be developmental precursors of the N170 in later childhood. The N170/N290 components are most prominent over right hemisphere, posterior midline and paramidline electrodes, and are likely related to the structural encoding of the physical features of the face, not recognition of a particular individual. The P400 is most prominent over posterior lateral leads and seems particularly sensitive to face orientation and features, evident from the fact that this component differs for inverted faces and distorted faces (de Haan 2008). The localization of these face-sensitive components can be inferred based on fMRI studies of face processing and the ERP scalp topography of the components as described above. From these studies, we know that face processing is largely generated in the inferior temporal cortex (i.e. fusiform gyrus) and superior temporal sulcus, areas that comes on-line in the first year of life (Itier and Taylor 2004).

A recent focus of interest in autism research has been the characterization of face processing in children with autism as a possible marker for deficits in social cognition. Several groups have speculated that impairment in social reciprocity may stem from abnormal early face processing. Multiple behavioral studies have shown abnormal face discrimination, recognition, and emotion perception in children and adults with autism (Boucher and Lewis 1992; Gepner 2004; Klin et al. 1999; Tantam et al. 1989). Behavioral evidence for reduced face preference has been shown in infancy as well. In a study of home videotapes of first birthday parties, the best predictor of developing

autism was a failure to attend to others' faces (Osterling and Dawson 1994).

Do these behavioral differences reflect abnormal neural circuitry underlying face perception? Furthermore, as discussed with language processing, if there is an impairment, is it in perception or in social cognition. In other words, are impairments in face processing rooted in an inability to integrate visual information into a conceptual whole, or does an early lack of interest in faces lead to a lack of cortical specialization for faces, which, in turn, results in impaired face processing?

As has been emphasized throughout this review, ERPs can shed some light on this question. Although the literature on face processing in autism has gained momentum in the past few years, the first ERP study to use face stimuli in autism was actually performed in 1971, using only two scalp electrodes. In this study, children with autism were compared to age matched, typical controls. Typical children differentiated stranger and mother's face based on more negative amplitude response to stranger, while the children with autism showed no difference in cortical response to the two stimuli (Small et al. 1971). Using high density ERP, impairments in face processing have now been well characterized by Dawson et al. In their first study (2002a, b), low functioning children with autism, ages 3–4, were compared to both IQ and age matched controls. Children were shown pictures of mother's face versus stranger's face, and in a comparison paradigm were shown familiar versus unfamiliar objects. As evidenced by their P400 and Nc, children with autism did not differentiate between mother and stranger, but did show differential response to unfamiliar objects as compared to familiar objects (Dawson et al. 2002a, b). In a re-analysis of this study, they found that there was an absence of the expected right hemispheric lateralization to faces in the children with developmental delay or autism, and that there were more negative responses to faces and faster responses to objects in the autism group. Interestingly, despite these ERP findings, the children were still able to differentiate objects from faces, suggesting that the processing differences did not impair simple recognition tasks. (Webb et al. 2006). These abnormalities have been demonstrated in high functioning adults as well. O'Connor et al. (2007) performed a face recognition paradigm in which faces and facial parts (eyes and mouth), as well as objects, were shown to adults with Asperger's syndrome and typical controls. The Asperger's adults exhibited slower N170 latencies to both faces and facial parts compared to controls, but did not show such a difference to objects (O'Connor et al. 2007).

Clearly these studies point towards a disturbance in the circuitry involved with face processing in children and perhaps adults with autism, with some suggestion that these

children do not show the same specialization for faces as do typical children and, instead, may show specialization for non-faces (objects). These studies suggest that the impairment is not simply one of perception. This contention finds further support in a recent study that found no differences between high functioning children with autism and typical controls in a paradigm reflecting the integrity of “visual feature integration” using a texture segregation task and a contour integration task (Kemner et al. 2007). Future studies that apply these face paradigms in infants at risk for autism will be invaluable in isolating the developmental root of this impairment in face processing.

Dawson’s group (2004) then investigated neural responses to emotion in autism. The N300 is an early component that is larger to fearful or angry faces and reflects increased allocation of attention to negative emotions. Its neural source is presumed to be the amygdala and its projections to prefrontal cortex. Using the same group of low functioning preschoolers with autism, compared to typical controls, children were shown pictures of a female face with either a neutral or fearful expression. Additionally, various behavioral observations were made using tasks centered on social orienting, joint attention, and response to distress. In this study, typical children showed the expected larger amplitude N300 response to fear faces compared to neutral, whereas the children with autism showed no differential response. Additionally, faster latency of the N300 in the autism group correlated with better joint attention, social orienting, and attention to social distress. These findings suggest that young children with autism may have impairments in emotion processing, which could have measurable behavioral consequences, such as time spent attending to others, specifically those expressing a negative emotion, and time dedicated to non-social orienting. (Dawson et al. 2004).

Since Dawson’s work, two other groups (O’Connor et al. 2005; Wong et al. 2008) have investigated emotion processing in autism and have not found ERP differences between autism and controls. However, both groups studied higher functioning children (and those with Asperger’s) and analyzed early components, namely the P1 and the N170. In the study by Wong, although ERP components were not different, source localization showed that activation of cortical regions important for face perception were delayed at “sub-second” latencies in the children with autism, both in the occipital and bitemporal sources.

The presence of the face inversion effect has been studied in high functioning adolescents and adults with autism. To briefly describe the face inversion effect, several behavioral studies have shown that older children and adults show a marked decrease in face recognition when the faces are inverted, and functional imaging has shown

reduced activation in face selective brain regions to inverted faces (Rossion and Gauthier 2002; Valentine 1988; Yovel and Kanwisher 2005). These findings have been used to support the argument that face recognition benefits from a “special” cortical process that is unique to upright faces, likely a result of experience in visualizing faces over the first few years of life. In the ERP inversion study in autism, adolescents and adults with high functioning autism and age matched controls were shown upright and inverted faces. Their task was a face recognition task. The group found that the autism group showed no difference in N170 latency between upright and inverted faces, unlike the control group where latency was longer for the inverted face. Thus, according to these studies, adolescents and adults with autism may process upright faces more slowly than neurotypical children and adults (McPartland et al. 2004), which suggests a lack of specificity in processing of upright faces in autism.

Several studies also have used ERPs to study gaze discrimination in autism and have found impairment in gaze detection, with no difference in neural response to direct or averted gaze, unlike typical controls (Grice et al. 2005; Senju et al. 2005). However, in these studies, which used full faces as stimuli, eye tracking was not performed in order to determine if, in fact, the autistic participants were looking at the eyes. Recently, an interesting study used a face with an averted gaze as the central cue in a modified flanker task (see section on executive function for description). In this study, high functioning children with autism did not show any differences in response to the facial stimulus in ERP activity compared to typical controls, and they showed similar reaction times to controls in both the congruent and incongruent task (Kemner et al. 2006). These studies suggest that perhaps children with autism have the capacity to process gaze change appropriately.

Finally, in an attempt to understand the effect of spatial frequency on face processing, Boeschoten et al. (2007) studied high functioning children with autism and typical controls. The stimuli consisted of faces, neutral objects, and objects of expertise, all of which were shown at high and low spatial frequency. Unlike many of the studies discussed in this section, they found *no* differences in the N170 between autism and controls, but did find differences in source modeling, with group differences found not in the posterior but in the frontal regions. Specifically, children with autism showed highest activation in posterior electrodes for all faces while controls had higher activation of frontal sources for the low spatial frequency faces (Boeschoten et al. 2007). This study suggests that even though scalp electrodes fail to demonstrate differences, there may be differences in processing at deeper cortical and sub-cortical levels.

Clearly there is aberrant face processing in autism, likely rooted in neural circuitry necessary for face recognition, emotion processing, feature discrimination, and holistic processing (as evidenced by the inversion effect). Areas critical for these tasks include, respectively, the fusiform gyrus, amygdala, and superior temporal sulcus. However, given the behavioral evidence that children show a preference for non-social stimuli (objects) to faces, we are reminded of Kuhl's language study in which preference for speech sounds was associated with more typical electrophysiological response to speech. In the face literature, given the wide range of studies, it is a bit difficult to discern whether the lack of experience with faces due to disinterest contributes to this abnormal neural circuitry, or whether it is a primary abnormality in visual perception. Likely the answer is the interplay of both areas, and we will consider this question further at the end of our review.

Executive Function

Executive function represents the cortical systems that manage other cognitive processes. It is thought to be involved in processes such as abstract thinking, planning, cognitive flexibility, rule acquisition, and implementation of appropriate actions.

These parameters can be difficult to measure behaviorally and, therefore, could be amenable to study using ERPs. Here we will describe the three studies that have applied ERPs to executive function tasks.

Strandburg et al. (1993) studied high functioning adults with autism with a *Continuous Performance Task* (CPT) and a *Span of Apprehension Task*. In the CPT, the participant responds whenever a number repeats in successive trials of an ongoing train of numbers. The task requires sustained attention and immediate memory. In the Span, the participant must identify which of two possible target letters is present in briefly presented 12-letter arrays and, therefore, requires rapid serial scanning as well as pattern recognition. The components of interest in this study were the CNV (continuous negative variation, reflecting early expectancy), N1 (early processing) and P3 (later processing). Results of the study showed that performance on these tasks was comparable between autism and controls, but that N1 and P3 amplitudes were larger in the autism group. The increased amplitudes may suggest that more effort is required to sustain performance on such tasks (Strandburg et al. 1993).

In the second executive function study using ERPs, Henderson et al. (2006) used a *Modified Flanker Task* to assess response monitoring in high functioning children with autism compared to age matched controls. Response monitoring refers to the ability to monitor and self-correct one's actions geared towards a pre-defined goal. There has

been behavioral evidence for impaired response monitoring in autism (Ozonoff and Jensen 1999; Pennington and Ozonoff 1996). In the task, participants are shown a row of arrows and asked to name the direction of the central arrow. Trials are either compatible (all arrows in same direction) or incompatible (central arrow in the opposite direction). Typically, in the incompatible trials reaction times are slower, with more errors made. The ERP component of interest is the Error Related Negativity (ERN), which reflects cortical monitoring of response accuracy. fMRI studies have shown that error monitoring is generated from the anterior cingulate gyrus and frontostriatal networks (Magno et al. 2006; Ullsperger and von Cramon 2006). In this study, the two groups performed equally and had equally large ERN amplitudes with error. However, the autism group showed longer latency in the ERN. When stratified based on verbal IQ and social functioning, those children with the highest amplitudes of ERNs had the highest verbal IQ and fewest symptoms of social impairment and anxiety. Therefore, rapid response monitoring may represent an adaptive skill that facilitates social and emotional development (Henderson et al. 2006). A third, recently published, study investigated the ERN in high functioning children with autism and typical controls. These authors also analyzed the error-related positivity (Pe), which has a centroparietal distribution and is likely generated from the anterior cingulate gyrus. Children were required to complete both a simple and difficult version of an auditory decision task, in which various animal sounds in succession were presented and children were required to respond with button presses. Children with autism had a smaller ERN and Pe and, behaviorally, they did not show the expected post-error slowing in reaction time that is seen in typical children. These findings suggest that children with autism may be less sensitive to situations where errors can happen and, in turn, they are unable to modify their behavior in such settings (Vlamings et al. 2008).

From these three studies, one could propose that neural circuits necessary for executive function may also be aberrant in children with autism and may correlate to dysfunction in social cognition. Clearly there is a broad scope for applying ERPs to the understanding of executive function in autism. One limitation to such studies is that they require a certain level of cognitive ability, thereby constraining the study population to higher functioning individuals.

ERP Implications for Our Understanding of Neural Circuitry in Autism

From both a behavioral and electrophysiological standpoint, it is clear that deficits in auditory and visual

processing, particularly social cognition, exist in individuals with autism. We can use the knowledge gained from ERP studies to consider whether these impairments are rooted in neural circuitry necessary for more general sensory processing, or whether the primary deficit lies in higher-level circuits involved with social cognition. Based on our review, the answer is probably both.

Let us consider the case of altered face processing, where deficits at multiple levels can lead to a similar endpoint: (a) low-level visual processing (occipital cortex and projections), (b) visuospatial attention/discrimination (striato-prefrontal networks, parieto-frontal networks), (c) working memory (rooted in hippocampus and projections) (d) higher-level recognition and discrimination of faces (fusiform gyrus, superior temporal sulcus) or (e) “social motivation” (rooted in the reward system: striatal-orbitofrontal cortex, nucleus accumbens). From the literature described above, it is likely that impairments in steps b through e are all implicated in aberrant face processing and that an interplay of these various deficits lead to the differences seen both behaviorally and electrophysiologically.

Overall ERP data suggest that low level visual processing is intact in autism. On the other hand, visuospatial attention and discrimination has been shown to be impaired in several ERP studies, with poorer performance on spatial discrimination tasks that correlate to ERP findings. These findings could be localized to impairment in striato-prefrontal cortical circuits. Next, while working memory has been less well studied in this population, one could look at the response to novel targets in the oddball paradigm as a marker for working memory. In multiple studies described in this review, reaction time and accuracy have been intact in high functioning individuals with autism, while ERP responses to the target stimuli have differed from normal controls, suggesting differences in novelty processing (putatively involving the hippocampus).

Finally, we can turn to the concept of “impaired social motivation,” postulated by Dawson et al. (2005), which refers to the possibility that individuals with autism lack pleasure in, or do not feel rewarded, when presented with social stimuli. Returning to the Kuhl study of language processing, children who preferred child-directed speech to non-speech had normal processing of speech sounds. One could speculate that an early lack of preference for mother’s voice could limit the experience of listening to speech, which could modify the neural circuitry necessary to process spoken language. This, in turn, could impair fundamental communication skills in autism. As we look to the future, it will be crucial to isolate behaviors that are localized to social motivation and rewards circuits, such as the amygdala, striato-orbitofrontal cortical circuits and nucleus accumbens-prefrontal cortical circuits, and then to study them using ERPs and MRI. An impaired reward system could lead

to an inability to learn from relevant social stimuli at a time when experience is critical for development of brain circuits necessary for social cognition.

The Future

Having reviewed the literature to date, and being equipped with some understanding of the strengths and weaknesses of ERPs in autism research, we now can look to the future and suggest ways in which this technology can be applied to a better definition of the autism spectrum disorders.

First, we must acknowledge the poor spatial resolution of ERPs while appreciating their outstanding temporal resolution, and perform more studies that couple ERPs with other forms of neuroimaging (i.e. high resolution MRI). In the autism literature to date, several studies have attempted to make structure/function associations by performing structural brain MRIs and then speculating on the association between structural differences and ERP findings (Salmond et al. 2007; Townsend et al. 2001). Such multimodal investigation is important when attempting to better characterize the neural dysfunction in these children.

Secondly, ERPs have the potential to be applied to the ongoing effort in defining endophenotypes within the autism spectrum. Endophenotypes refer to pre-behavioral traits, and can be characterized by neuropsychological, biochemical, neuroanatomical, or cognitive markers, all of which likely contribute to the behavior being studied. In behavioral disorders such as autism, where the diagnostic behaviors are extremely broad and heterogeneous, endophenotypes may help us to understand gene-behavior associations and the mediating effects of genes on behaviors, (Duvall et al. 2007; Losh and Piven 2007; Spence et al. 2006; Viding and Blakemore 2007).

Recently, the search for endophenotypes has led to the definition of the “Broader Autism Phenotype,” in which certain impairments in joint attention, language, and social interaction have been isolated in “typical” family members of children with autism (Bailey and Parr 2003; Bishop et al. 2006; Bolte et al. 2007; Bolte and Poustka 2006; Dawson et al. 2002a, b, 2007; Ruser et al. 2007; Scheeren and Stauder 2007; Stone et al. 2007; Sullivan et al. 2007; Sung et al. 2005). In one representative study, Dawson’s group performed a study of face processing using ERPs in parents of children with autism and found, behaviorally and electrophysiologically, that parents of children with autism did not show the expected preference for faces over objects. Additionally, these parents, unlike parents of typical children, showed no difference in N170 latency between faces and objects. The search for the genetic source of this impaired face processing is currently under investigation, but such studies may guide our understanding of the neural

and genetic bases of the core deficits that define autism or, at least, the early susceptibility to the autism phenotype.

An excellent example in the psychiatry literature of the definition of an endophenotype using genetics, ERP, neuroimaging, and behavioral testing, is the work focusing on the serotonin transporter gene and its association to mood disorders and personality traits, most robustly studied in social anxiety and shyness in children (Battaglia et al. 2005; Canli and Lesch 2007; Gunthert et al. 2007; Hayden et al. 2007; Serretti et al. 2006). Two common alleles of the serotonin transporter promoter (5-HTTPR), short and long, have been differentially associated with: level of serotonin uptake and transport, amygdala activity in response to angry or fearful faces, and behavioral phenotypes such as anxiety, avoidant personalities and shyness. In a recent study, school children were characterized by degree of shyness using questionnaires, and were tested for the 5-HTTPR allele lengths. Then they were shown pictures of happy, neutral, and angry faces while ERPs were recorded. A significant expression-genotype interaction was found. Children who were shy were most likely to have more 1 or 2 copies of the short allele of the 5-HTTPR, and to have smaller N400 amplitudes to angry and neutral faces (Battaglia et al. 2005). One could imagine taking this work a step further by using emotion ERP paradigms coupled with genetic testing early in infancy to define children at risk for anxiety disorder, and then targeting early behavioral interventions to prevent social phobias.

Endophenotypes also may help us to predict the development of the aberrant behaviors far before they have emerged clinically. ERPs can isolate pre-behavioral neural markers and can be performed in very young children and, therefore, could be quite useful in the creation of endophenotypes. Several examples have been given throughout this review, such as the possibility that the presence of a large MMN to speech sounds may contribute to (or predict) receptive language impairment. To continue along these lines, if one were to define endophenotypes that could be detected early in life (such as in a high risk sibling of a child with autism), then informed interventions could be created that would target the specified deficit. For example, it may be found that those children with enhanced MMN to pitch changes show a significant hypersensitivity to certain sounds in the environment, including certain speech sounds, which then translates to an avoidance of spoken language and resulting profound impairment in receptive language skills. With this insight gained from the ERP data, one could design a language-based therapy that would regulate auditory input to children in order to make language reception more tolerable, which could facilitate their receptive language development.

McPartland and Dawson (2004) drew a similar conclusion in their study of the face inversion effect in autism, in

which they concluded, “early behavioral indices of face processing provide a potential marker for recognizing autism (and)...also provides a viable avenue for interventions. Given the possibility of a critical period for the development of face processing expertise, it may be important to incorporate face-processing strategies into early intervention program.” Thus, by providing at-risk infants and young children with the opportunity to develop face “expertise” one may be able to obviate, or at least attenuate, the development of impairment in reciprocal social interaction that defines autism.

Conclusion

In this paper we have attempted to critically review the ERP literature that investigates the neural correlates of behavioral impairments in autism. We have discussed low-level and higher cognitive processing of auditory and visual stimuli in autism, and social cognition in each sensory domain. ERP evidence for differences in auditory and visual stimulus orientation, attention, information storage, and novelty detection, as well as in language and face processing, exist, with several studies also demonstrating the preference for non-social stimuli. The majority of studies have targeted high functioning, older children or adolescents with autism, but several recent studies have used ERPs to characterize low functioning preschool children, particularly in the domain of face processing.

As emphasized throughout this review, what has been refreshing in this area of research is the consistent effort to use ERPs to elucidate the neural sources of the *core deficits* in autism. As we look to the future, we should capitalize on the temporal resolution of this technique, as well as its applicability to developmental populations, and couple ERPs with other forms of advanced neuroimaging to better define early neural markers and endophenotypes of the autism spectrum. Only through such multimodal investigation will we be able to understand the mechanisms and neural substrates underlying the impairments in language and social cognition that define autism and, with this knowledge, begin to create informed and targeted interventions.

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